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(54) Title: METHOD AND REAGENT FOR PREVENTION, INHIBITION OF PROGRESSION AND REGRESSION OF VASCULAR DISEASES

(57) Abstract

A nucleic acid molecule which blocks synthesis and/or expression of mRNAs associated with initial development, progression or regression of vascular disease. In particular are provided ribozyme sequences which cleave human or rabbit cholesterol ester transfer protein (CETP) mRNAs.

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DESCRIPTION

Method and Reagent for Prevention, Inhibition of Progression and Regression of Vascular Diseases

Background Of The Invention

This invention relates to the methods for the prevention, inhibition of progression and regression of vascular diseases, in particular, inhibition of cholesterol ester transfer protein (CETP) inhibition.

The following is a discussion of relevant art, none of which is admitted to be prior art to the present invention.

Vascular diseases, which includes etiologies such as peripheral vascular disease, coronary heart disease (CHD), stroke and restenosis, remain the leading cause of death and disability in the United States and throughout the world. In 1990 alone, approximately 500,000 people died in the United States from CHD. Although, diet and life style can accelerate the rate of onset of vascular diseases, genetic predisposition leading to "dyslipidemia" is a major and significant factor attributing to vascular related deaths and disabilities (Anderson et al., 1987 JAMA 257, 2176). By "dyslipidemia" is meant abnormal levels of lipoproteins in plasma.

A variety of risk factors have been identified that are associated with increased risk of vascular disease (Barr et al., 1951 Am. J. Med. 11, 480; Kannel et al., 1971 Ann. Intern. Med. 74, 1; Miller et al., 1975 Lancet 1, 16; Levy et al., 1984 Circulation 69, 325.; Lipid Research Clinics Program, 1984 JAMA 251, 351; Lipid Research Clinics Program, 1984 JAMA 251, 365; Anderson et al., 1987 JAMA 257, 2176; Blankenhorn et al., 1987 J. Am. Med. Assoc. 257, 3233.; Frick et al., 1987 N. Engl. J. Med. 317, 1237; Expert Panel, 1988 Arch. Intern. Med. 148, 36.; Grundy et al., 1989 Arch. Intern. Med. 149, 505.; La Rosa, 1990 Am. J. Cardiol. 65, 7F-10F). Among these are

the dyslipidemias of high levels of low density lipoproteins (LDL) and low levels of high density lipoproteins (HDL), singly or in combination. Often the ratio of HDL cholesterol to that of LDL cholesterol is used to assess risk of vascular disease. Thus, a high ratio of HDL/LDL cholesterol is desirable, and intervention to increase the ratio by lowering LDL and elevating HDL, singly or in combination is desirable.

Familial hypercholesterolemia (FH), a genetic disorder caused by defective or deficient LDL receptors presents as a marked elevation in LDL and risk in vascular disease (Goldstein et al., 1989 "Familial hypercholesterolemia" In: The Metabolic Basis of Inherited Diseases, 6th Ed., Schiver, C.R., Beaudet, A.L., Sly, W.S., and Valle, D. editors, 1215). Homozygous FH is a relatively rare disorder (1 in 1,000,000). Homozygous FH patients have extremely high levels of LDL with very short life expectancies. Therapy for these individuals include liver transplantation and LDL plasmaphoresis. Heterozygous FH is relatively common disorder (1 in 500). Heterozygous FH patients present with LDL levels approximately twice normal and are at risk for developing premature atherosclerosis followed by the common sequelae associated with vascular diseases, including myocardial infarction and stroke. Conventional therapy for heterozygous FH patients generally includes HMG CoA reductase inhibitors alone or in combination with bile acid sequestrants. Human prospective trials have demonstrated reduction in CHD related endpoints in hypercholesterolemic subjects treated with HMGCoA reductase inhibitors, bile acid sequestrants, Nicotinic acid, and gemfibrozil (La Rosa, 1990 Am. J. Cardiol. 65, 7F; Pedersen et al., 1994 Lancet 344, 1383).

Other conditions, such as apoE 3/4 and apoE4/4 genotype are also associated with increased LDL elevation and risk of CHD. However the direct causal relation between apoE4 polymorphism, elevated LDL and increased risk is unknown (Davignon et al., 1988 Arteriosclerosis 8, 1;

Dallongeville et al., 1992 J. Lipid Res. 33, 447; Walden et al., 1994 Ann. Intern. Med. 120, 1026).

Low levels of HDL or hypoalphalipoproteinemia is a relatively common condition. The genetic basis for hypoalphalipoproteinemia is poorly understood, but likely results from multiple factors related to genetic predisposition and life style. Numerous prospective and retrospective studies have shown that HDL is inversely and strongly correlated with vascular disease. Therefore treatment to elevate HDL levels is warranted (Grundy et al., 1989 Arch. Intern. Med. 149, 505). It is also well recognized, that plasma triglyceride elevation is generally associated with low HDL levels, and insulin resistance (Reaven, 1988 Diabetes 37, 1595). Conventional therapies for elevated triglycerides and low HDL generally include treatment with fibrates. Gemfibrozil, a compound of this class, effectively lowers plasma triglycerides, and moderately elevates HDL (Frick, 1987 N. Engl. J. Med. 317, 1237). In a large human prospective trial, gemfibrozil has been shown to cause a significant reduction in vascular endpoints (Frick, 1987 supra).

The process termed reverse cholesterol transport (RCT; Bailey, 1965 Exp. Cell. Res. 37, 175; Glomset, 1968 J. Lipid Res. 9, 155) is a mechanism resulting in a net efflux of cholesterol present in peripheral tissues for disposal in bile. This multistep "hypothesized" pathway invokes removal of cholesteryl from peripheral tissues to HDL. Lecithin: cholesterol acyltransferase (LCAT), a circulating plasma enzyme, primarily mediates the esterification of HDL cholesterol to cholesteryl esters. CETP, also present in plasma, mediates HDL cholesteryl ester net transfer to apolipoprotein B (apoB)-containing lipoproteins including very low density lipoproteins (VLDL), intermediate density lipoproteins or remnants (IDL) and LDL. CETP-mediated cholesteryl ester enrichment of the LDL precursors, VLDL and IDL, ultimately contributes to the cholesterol content of LDL. Hepatic receptor-mediated

LDL uptake, and a net flux of these delivered cholesteryl esters to the bile acid pool completes RCT. However, species that lack CETP (Oschry et al., 1982 J. Lipid Res. 23, 1099) or humans deficient in CETP (Koizumi et al., 1985 Atherosclerosis 58, 175) are unable to effectively transfer cholesteryl esters formed in HDL to the LDL precursor pool. Although the break in this link of the RCT pathway might predictably result in a marked deficiency in peripheral tissue cholesterol egress, surprisingly, this is not the case. In CETP deficient species, the HDL cholesteryl ester pool accumulates at the expense of the LDL pool. The HDL particles become enlarged and apoA-I, apoA-IV, and apoE-enriched (Brown et al., 1989 Nature 342, 448-451; Yamashita et al., 1990 J. Clin. Invest. 86, 688; Bisgaier et al., 1991 J. Lipid Res. 32, 21). Particles containing apoE can effectively be delivered to the liver as whole particles by facilitated mechanisms, including those utilizing the LDL receptor and the LDL receptor related protein (LRP) (Goldstein et al., 1985 Ann. Rev. Cell Biol. 1, 1; Mahley, 1988 Science 240, 622.; Beisiegel et al., 1989 Nature 341, 162; Bisgaier et al., 1989 J. Biol. Chem. 264, 862.). Thus, alternative mechanisms exist that facilitate tissue cholesterol egress and delivery of non-LDL cholesterol to liver in the absence of CETP.

Thus, CETP inhibition may inhibit or eliminate the RCT pathway thereby preventing the reduction in size and density of HDL, prolonging HDL half-life, and resulting in increased HDL levels. Additionally, the lack of transport of cholesteryl esters from HDL to apoB-containing lipoproteins may reduce LDL concentrations. Both these effects would result in an elevation of the HDL to LDL ratio. As high HDL/LDL ratios and HDL levels have been associated with anti-atherogenicity, diminishing CETP activity may prevent or inhibit progression and regression of vascular disease.

CETP is a 74 kDa glycoprotein that facilitates neutral lipid (cholesteryl esters and triglycerides) transfer between plasma lipoproteins (Zilversmit et al., 1975 Biochim. Biophys. Acta 409, 393; Ha et al., 1982 Comp. Biochem. Physiol. 71B, 265; Drayna et al., 1987 Nature 327, 632; Hesler et al., 1987 J. Biol. Chem. 262, 2275; Swenson et al., 1987 J. Biol. Chem. 262, 16271; Hesler et al., 1988 J. Biol. Chem. 263, 5020; Nagashima et al., 1988 J. Lipid Res. 29, 1643; Pape et al., 1991 Arterioscler. Thromb. 11, 1759). In non-human primates and rabbits, hepatic non-parenchymal cells are likely the major synthetic source of CETP (Pape et al., 1991 Arterioscler. Thromb. 11, 1759; Pape et al., 1991 J. Biol. Chem. 266, 12829; Rea et al., 1993 J. Lipid Res. 34, 1901), in that these cells have the highest cellular content of CETP mRNA relative to total RNA. Abundant amounts of CETP mRNA has also been shown in hepatic parenchymal cells, adipose, and spleen and to a lesser extent in the intestine and heart.

The level of CETP activity between species is highly variable (Ha et al., 1982 Comp. Biochem. Physiol. 71B, 265; Bisgaier et al., 1993 J. Lipid Res. 34, 1625). In general, species with high CETP activity (e.g., humans and rabbits) are susceptible to dietary induced atherosclerosis, while species with little or no CETP activity (e.g., mice, rats and dogs) are resistant (Koizumi et al., 1985 Atherosclerosis 58, 175; Inazu et al., 1990 N. Engl. J. Med. 323, 1234; Agellon et al., 1991 J. Biol. Chem. 260, 10796; Bisgaier et al., 1991 J. Lipid Res. 32, 21; Marotti et al., 1992 Arterioscler. Thrombosis 12, 736). Likewise, those species with little or no CETP activity have anti-atherosclerotic lipoprotein profiles: plasma HDL levels are elevated and LDL are reduced (Ha et al., 1982 Comp. Biochem. Physiol. 71B, 265). Infusions of inhibitory CETP monoclonal or polyclonal antibodies into rabbits or infusion of CETP into rats will invert the lipoprotein profiles (Ha et al., 1985 Biochim. Biophys. Acta. 833,

203; Abbey et al., 1989 Biochim. Biophys. Acta 1003, 20; Groener et al., 1989 Biochim. Biophys. Acta 1002, 93; Whitlock et al., 1989 J. Clin. Invest. 84, 129.). Unlike control mice of similar genetic background, CETP transgenic mice develop atherosclerotic lipoproteins and atherosclerosis (Marotti et al., 1992 Arterioscler. Thromb. 12, 736).

Recent studies of a Japanese family have shown that a deficiency in plasma CETP associated with marked elevation of HDL, its associated apolipoproteins (apoA-I, apoE, apoA-IV) and a rarity of coronary artery disease (Koizumi et al., 1985 Atherosclerosis 58, 175; Brown et al., 1989 Nature 342, 448; Inazu et al., 1990 N. Engl. J. Med. 323, 1234; Bisgaier et al., 1991 J. Lipid Res. 32, 21.; Ikewaki et al., 1991 Arterioscler. Thromb. 11, 1400a; Koizumi et al., 1991 Atherosclerosis 90, 189). These individuals were identified through routine cholesterol screening and have no other hyperlipidemia related disease. The defect has been identified as a G to A substitution in the fourteenth intron of CETP pre-messenger ribonucleic acid (RNA) (Brown et al., 1989 Nature 342, 448). This splice donor defect is also the cause of the deficiency in additional Japanese families (Inazu et al., 1990 N. Engl. J. Med. 323, 1234; Koizumi et al., 1991 Atherosclerosis 90, 189; Hirano et al., 1993 Atherosclerosis 100, 85). In a more recent study, the deficiency (both homozygous and heterozygous) has been shown to be associated with a large proportion of Japanese with hyperalphalipoproteinemia (Inazu et al., 1992 Horm. Metab. Res. 24, 284; Hirano et al., 1993 Atherosclerosis 100, 85). A missense mutation at nucleotide 1506 (G for A) also has been identified in exon 15 of the CETP gene, resulting in a substation of a glycine for aspartic acid at amino acid 442 (Takahashi et al., 1993 J. Clin. Invest. 92, 2060). The two subjects heterozygous for the missense mutation had three times the normal HDL levels. Overall these studies suggest that even partial reduction in CETP levels, as found in

heterozygous individuals, is associated with elevated HDL. This apparently benign condition (CETP deficiency) has been coined the "longevity syndrome" (Koizumi et al., 1985 Atherosclerosis 58, 175).

Although CETP facilitates an equimolar exchange of neutral lipids, net transfer of cholesteryl ester to LDL occurs due to (1) concentration and core lipid composition of exchange partners and (2) residence time of lipoproteins (Nichols et al., 1965 J. Lipid. Res. 206; Pattnaik et al., 1978 Biochim. Biophys. Acta 530, 428; Barter et al., 1979 Metabolism 28, 230). Under basal conditions (i.e., overnight fast), CETP facilitates transfer below maximal velocity, while postprandially CETP appears to facilitate transfer at or near maximal velocity (Tall et al., 1986 J. Clin. Invest. 77, 1163; Mann et al., 1991 J. Clin. Invest. 88, 2059; Bisgaier et al., 1993 J. Lipid Res. 34, 1625). It is also likely, but has not been systematically shown, that individuals with elevated triglycerides would have elevated CETP activity (but not necessarily increased CETP mass). In general, these subjects have reduced levels of HDL and elevated LDL. These consequences, in part may be the result of events facilitated by CETP.

The complete amino acid sequence of human, rabbit, cynomolgus monkey and hamster CETP are known (Drayna et al., 1987 Nature 327, 632; Nagashima et al., 1988 J. Lipid Res. 29, 1643; Jiang et al., 1991 J. Biol. Chem. 266, 4631; Pape et al., 1991 Arterioscler. Thromb. 11, 1759). Human plasma levels are approximately 1-2 μg/ml, while rabbit levels are approximately 4 μg/ml. Cholesterol feeding in rabbits elevates tissue CETP mRNA, plasma CETP, and maximal plasma activity approximately 4 fold (Quinet et al., 1990 J. Clin. Invest. 85, 357; McPherson et al., 1991 Arterioscler. Thromb. 11, 797). The protein is stable to heat, limited proteolysis, but not oxidation. CETP has been mapped with neutral and inhibitory monoclonal antibodies and by site-directed mutagenesis

(Hesler et al., 1987 J. Biol. Chem. 262, 2275; Hesler et al., 1988 J. Biol. Chem. 263, 5020; Wang et al., 1991 Biochemistry 30, 3484). Stable transfection of the human gene in CHO cells has been accomplished (Wang et al., 1991 Biochemistry 30, 3484; Wang et al., 1992 J. Biol. Chem. 267, 17487). However, the protein has not been crystallized nor have the lipid binding domains been identified. Furthermore, the mechanisms by which CETP facilitates transfer are poorly understood.

Direct pharmacological inhibition of the existing protein in plasma or targeting CETP gene expression might lead to reduced plasma activity and result in a beneficial lipoprotein profile (i.e., HDL elevation and LDL diminution) and a reduced risk of coronary heart disease. However a synthetic compound approach for the direct inhibition of the plasma CETP has not yet been promising (Bisgaier et al., 1994 Lipids 29).

The gene encoding CETP is composed of 16 exons of various sizes (32-250 bp) and spans approximately 25 kb on the long arm (q12-21) of chromosome 16 (Lusis et al., 1987 Genomics 1, 232; Agellon et al., 1990 Biochemistry 29, 1372). Cloning and sequencing of the human CETP cDNA has been reported and shown to contain an open reading frame and 3' untranslated region of 1656 nucleotides in length (Drayna et al., 1987 Nature 327, 632). Analysis of amino-acid and nucleic acid sequence has indicated a protein that is unique among eukaryotic species. A pentanucleotide amino acid stretch in the precursor protein signal peptide of CETP is conserved among the lipid metabolism associated proteins, for example apoA-IV, apoA-I, and lipoprotein lipase (Agellon et al., 1990 Biochemistry 29, 1372). This conservation occurs at both the nucleotide and the amino-acid level. This small but highly conserved region is found only in the precursor protein species and is removed before secretion of the mature protein into the blood stream. Other less conserved homologies have been noted with two lipopolysaccaride binding proteins, bac-

terial permeability increasing protein found in leukocyte granules and plasma lipopolysaccharide binding protein (Tall, 1993 J. Lipid Res. 34, 1255).

A single predominant splicing variant of the CETP message has been identified and characterized. This variant CETP mRNA lacks exon 9 and accounts for between 14-46% of total CETP mRNA with the highest percentage of this variant seen in the spleen. While the function of this abundant splice variant is not clearly understood, when coordinately expressed with full-length CETP in Chinese Hamster Ovary (CHO) cells, it was shown not to be secreted and capable of inhibiting secretion of the full length CETP protein (Quinet et al., 1993 J. Biol. Chem. 268, 16891).

A consequence of inhibiting CETP, besides that of favorably increasing the HDL/LDL cholesterol ratio, is a change in the distribution and level of apoE. In species lacking CETP (e.g., rats), during monoclonal antibody induced inhibition of CETP in hamsters, and in human CETP deficiency, plasma apoE levels are elevated (Yamashita et al., 1990 J. Clin. Invest. 86, 688; Eto et al., 1990 Artery 17, 202; Hirano et al., 1993 Atherosclerosis 100, 85; Takahashi et al., 1993 J. Clin. Invest. 92, 2060; Bisgaier et al., 1991 J. Lipid Res. 32, 21; Evans et al., 1994 J. Lipid Res. 35, 1634). Furthermore, HDL apoE-enrichment was observed (Evans et al., 1994 J. Lipid Res. 35, 1634). Recent in vitro studies have revealed mechanisms by which apoE-enriched HDL are protective (Yamada et al., 1992 J. Clin. Invest. 706; Saxena et al., 1993 J. Biol. Chem. 268, 14812). Additional studies have also demonstrated that apoE deficiency causes profound and accelerated rates of atherosclerosis in mice, a species not normally susceptible to atherosclerosis (Plump et al., 1992 Cell 71, 343; Zhang et al., 1992 Science 258, 468). Thus an expected and desirable consequence of CETP inhibition includes elevation of apoE-rich HDL. In apoE deficiency, overexpression of apoA-I can also afford protec-

tion against atherosclerosis (Plump et al., 1994 Proc. Natl. Acad. Sci. USA 91, 9607), and elevation of this protein is also an expected consequence of CETP inhibition (Koizumi et al., 1985 Atherosclerosis 58, 175; Eto et al., 1990 Artery 17, 202; Hirano et al., 1993 Atherosclerosis 100, 85; Takahashi et al., 1993 J. Clin. Invest. 92, 2060).

There currently exists no practical therapeutic treatment for interfering with or blocking CETP activity in humans. Although not practical, repetitive anti-CETP combined with anti-LDL plasmaphoreseis resulted in favorable changes in LDL and HDL levels and HDL/LDL ratios in a limited number of human studies (Davidson, U.S. Patent 5,279,540). Although plasma CETP levels markedly decreased with duration of plasmaphoresis treatments, neither anti-CETP plasmaphoresis alone nor control non-immune plasmaphoresis data were reported. Several potential inhibitors are being explored in various laboratories. These inhibitors include monoclonal antibodies and an inhibitor protein recently found in baboon plasma tentatively identified as the N-terminal fragment of apolipoprotein C-I (Kushwaha et al., 1993 J. Lipid Res. 1993, 1285; Kushwaha et al., WO 93/11782). In the current application, a ribozyme, antisense or 2-5A-antisense or triplex DNA approach is described. The advantage of these approaches is their ability to selectively target specific regions of the CETP mRNA.

Summary Of The Invention

The invention features novel nucleic acid-based techniques [e.g., enzymatic RNA molecules (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA] and methods for their use for: (1) treatment of dyslipidemias by decreasing lipoproprotein risk factors, in particular, decreasing high levels of LDL or increasing low levels of HDL, or a combination of both and (2) for the prevention, inhibition of progression, and regression

of vascular diseases, particularly, those diseases associated with (but not limited to) peripheral vascular disease, coronary heart disease, stroke, vascular complications of diabetes, transplant, atherectomy, and angioplastic restenosis.

The uniqueness of the CETP coding region and protein afford an increased safety margin when contemplating sequence-specific therapeutics targeting of the mRNA, such as ribozymes or antisense nucleic acids or 2-5A antisense chimeras, since there would be a reduced likelihood of non-specific activity from these therapeutics.

In a preferred embodiment, the invention features use of nucleic acid-based techniques to treat lipoprotein risk factors and/or prevent vascular diseases by inhibiting the synthesis of cholestryl ester transfer protein (CETP).

Those in the art will recognize the other potential targets, for e.g., apolipoprotein B, are also suitable for treatment with nucleic acid-based techniques described in the present invention.

By "inhibit" is meant that the activity of CETP or level of mRNAs encoded by CETP is reduced below that observed in the absence of the nucleic acid, particularly, inhibition with ribozymes and preferably is below that level observed in the presence of an inactive RNA molecule able to bind to the same site on the mRNA, but unable to cleave that RNA.

By "enzymatic nucleic acid (NA) molecule" it is meant a nucleic acid molecule which has complementarity in a substrate binding region to a specified gene target, and also has an enzymatic activity which is active to specifically cleave RNA in that target. That is, the enzymatic nucleic acid molecule is able to intermolecularly cleave RNA and thereby inactivate a target RNA molecule. This complementarity functions to allow sufficient hybridization of the enzymatic nucleic acid molecule to the target RNA to allow the cleavage to occur. One hundred percent

complementarity is preferred, but complementarity as low as 50-75% may also be useful in this invention.

By "equivalent" RNA to CETP is meant to include those naturally occurring RNA molecules associated with cardiovascular diseases in various animals, including human, rabbit and monkey. Such a molecule will generally contain some ribonucleotides, but the other nucleotides may be substituted at the 2'-hydroxyl position and in other locations with other moieties as discussed below.

By "antisense nucleic acid" is meant a non-enzymatic nucleic acid molecule that binds to another RNA (target RNA) by means of RNA-RNA or RNA-DNA or RNA-PNA (protein nucleic acid; Egholm et al., 1993 Nature 365, 566) interactions and alters the activity of the target RNA (for a review see Stein and Cheng, 1993 Science 261, 1004).

By "2-5A antisense chimera" is meant, an antisense oligonucleotide containing a 5' phosphorylated 2'-5'-linked adenylate residues. These chimeras bind to target RNA in a sequence-specific manner and activate a cellular 2-5A-dependent ribonuclease which in turn cleaves the target RNA (Torrence et al., 1993 Proc. Natl. Acad. Sci. USA 90, 1300).

By "triplex DNA" is meant an oligonucleotide that can bind to a double-stranded DNA in a sequence-specific manner to form a triple-strand helix. Triple-helix formation has been shown to inhibit transcription of the targeted gene (Duval-Valentin et al., 1992 Proc. Natl. Acad. Sci. USA 89, 504).

By "gene" is meant a nucleic acid that encodes an RNA.

By "complementarity" is meant a nucleic acid that can form hydrogen bond(s) with other RNA sequence by either traditional Watson-Crick or other non-traditional types (for example, Hoogsteen type) of base-paired interactions.

Six basic varieties of naturally-occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds in trans (and thus can

cleave other RNA molecules) under physiological conditions. Table I summarizes some of the characteristics of these ribozymes. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over other technologies, since the concentration of ribozyme necessary to affect a therapeutic treatment is lower. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base-pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme.

Ribozymes that cleave the specified sites in CETP mRNAs represent a novel therapeutic approach to vascular disease. Applicant indicates that ribozymes are able to inhibit the activity of CETP and that the catalytic activity of the ribozymes is required for their inhibitory effect. Those of ordinary skill in the art, will find that it is clear from the examples described that other ribozymes that cleave these sites in CETP mRNAs may be readily designed and are within the invention.

In preferred embodiments of this invention, the enzymatic nucleic acid molecule is formed in a hammerhead or hairpin motif, but may also be formed in the motif of a hepatitis delta virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA. Examples of such hammerhead motifs are described by Rossi et al., 1992, Aids Research and Human Retroviruses 8, 183, of hairpin motifs by Hampel et al., EP0360257, Hampel and Tritz, 1989 Biochemistry 28, 4929, and Hampel et al., 1990 Nucleic Acids Res. 18, 299, and an example of the hepatitis delta virus motif is described by Perrotta and Been, 1992 Biochemistry 31, 16; of the RNaseP motif by Guerrier-Takada et al., 1983 Cell 35, 849, Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, 1990 Cell 61, 685-696; Saville and Collins, 1991 Proc. Natl. Acad. Sci. USA 88, 8826-8830; Collins and Olive, 1993 Biochemistry 32, 2795-2799) and of the Group I intron by Cech et al., U.S. Patent 4,987,071. These specific motifs are not limiting in the invention and those skilled in the art will recognize that all that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule.

In a preferred embodiment the invention provides a method for producing a class of enzymatic cleaving agents which exhibit a high degree of specificity for the RNA of a desired target. The enzymatic nucleic acid molecule is preferably targeted to a highly conserved sequence region of a target mRNAs encoding CETP proteins such that specific treatment of a disease or condition can be provided with either one or several enzymatic nucleic acids. Such enzymatic nucleic acid molecules can be delivered exogenously to specific cells as required. Alternatively, the

ribozymes can be expressed from DNA/RNA vectors that are delivered to specific cells.

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small enzymatic nucleic acid motifs (e.g., of the hammerhead or the hairpin structure) are used for exogenous delivery. The simple structure of these molecules increases the ability of the enzymatic nucleic acid to invade targeted regions of the mRNA structure. However, these catalytic RNA molecules can also be expressed within cells from eukaryotic promoters (e.g., Scanlon et al., 1991, Proc. Natl. Acad. Sci. USA, 88, 10591-5; Kashani-Sabet et al., 1992 Antisense Res. Dev., 2, 3-15; Dropulic et al., 1992 J. Virol, 66, 1432-41; Weerasinghe et al., 1991 J. Virol, 65, 5531-4; Ojwang et al., 1992 Proc. Natl. Acad. Sci. USA 89, 10802-6; Chen et al., 1992 Nucleic Acids Res., 20, 4581-9; Sarver et al., 1990 Science 247, 1222-1225). Those skilled in the art realize that any ribozyme can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such ribozymes can be augmented by their release from the primary transcript by a second ribozyme (Draper et al., PCT WO 93/23569, and Sullivan et al., PCT WO 94/02595, both hereby incorporated in their totality by reference herein; Ohkawa et al., 1992 Nucleic Acids Symp. Ser., 27, 15-6; Taira et al., 1991, Nucleic Acids Res., 19, 5125-30; Ventura et al., 1993 Nucleic Acids Res., 21, 3249-55; Chowrira et al., 1994 J. Biol. Chem. 269, 25856).

Such ribozymes are useful for the prevention of the diseases and conditions discussed above, and any other diseases or conditions that are related to the level of CETP activity in a cell or tissue. By "related" is meant that the inhibition of CETP mRNAs and thus reduction in the level of protein activity will relieve to some extent the symptoms of the disease or condition.

Ribozymes are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues ex vivo, or in vivo through injection, infusion pump or stent, with or without their incorporation in biopolymers. In preferred embodiments, the ribozymes have binding arms which are complementary to the sequences in Tables II, IV, VI and VII. Examples of such ribozymes are shown in Tables III, V, VI and VII. Examples of such ribozymes consist essentially of sequences defined in these Tables. By "consists essentially of" is meant that the active ribozyme contains an enzymatic center equivalent to those in the examples, and binding arms able to bind mRNA such that cleavage at the target site occurs. Other sequences may be present which do not interfere with such cleavage.

In another aspect of the invention, ribozymes that cleave target molecules and inhibit CETP activity are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors are preferably DNA plasmids or viral vectors. Ribozyme expressing viral vectors could be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the recombinant vectors capable of expressing the ribozymes are delivered as described above, and persist in target cells. Alternatively, viral vectors may be used that provide for transient expression of ribozymes. Such vectors might be repeatedly administered as necessary. Once expressed, the ribozymes cleave the target mRNA. Delivery of ribozyme expressing vectors could be systemic, such as by intravenous or intramuscular administration, by administration to target cells explanted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

In a preferred embodiment nucleic acids targeted to Exon 9 of CETP gene is described. A single predominant alternate-splicing variant of the CETP message that lacks exon 9 has been identified and characterized (Inazu et al., 1991 Biochemistry 31, 2352; Quinet et al., 1993 J. Biol. Chem. 268, 16891). While the function of this abundant splice variant is not clearly understood, it is known to be not secreted and capable of inhibiting secretion of the full-length CETP protein. (Quinet et al. 1993 J. Biol. Chem. 16891). Inhibition of full-length CETP secretion is believed to occur due to a heterodimeric complex formation between the full-length and the spliced variant of CETP. This suggests that the spliced variant of CETP might be beneficial in regulating the plasma level of CETP. Nucleic acid-based therapeutics of this invention, therefore, may be selectively targeted to block the expression of exon 9-containing CETP.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description Of The Preferred Embodiments

The drawings will first briefly be described.

Drawings

Figure 1 is a diagrammatic representation of the hammerhead ribozyme domain known in the art. Stem II can be ≥ 2 base-pair long.

Figure 2a is a diagrammatic representation of the hammerhead ribozyme domain known in the art; Figure 2b is a diagrammatic representation of the hammerhead ribozyme as divided by Uhlenbeck (1987, Nature, 327, 596-600) into a substrate and enzyme portion; Figure 2c is a similar diagram showing the hammerhead divided by Haseloff and Gerlach (1988, Nature, 334, 585-591) into two portions;

and Figure 2d is a similar diagram showing the hammerhead divided by Jeffries and Symons (1989, Nucl. Acids. Res., 17, 1371-1371) into two portions.

Figure 3 is a diagrammatic representation of the general structure of a hairpin ribozyme. Helix 2 (H2) is provided with a least 4 base pairs (i.e., n is 1, 2, 3 or 4) and helix 5 can be optionally provided of length 2 or more bases (preferably 3 - 20 bases, i.e., m is from 1 - 20 or more). Helix 2 and helix 5 may be covalently linked by one or more bases (i.e., r is ≥ 1 base). Helix 1, 4 or 5 may also be extended by 2 or more base pairs (e.g., 4 - 20 base pairs) to stabilize the ribozyme structure, and preferably is a protein binding site. In each instance, each N and N' independently is any normal or modified base and each dash represents a potential base-pairing interaction. These nucleotides may be modified at the sugar, base or phosphate. Complete base-pairing is not required in the helices, but is preferred. Helix 1 and 4 can be of any size (i.e., o and p is each independently from 0 to any number, e.g., 20) as long as some base-pairing is maintained. Essential bases are shown as specific bases in the structure, but those in the art will recognize that one or more may be modified chemically (abasic, base, sugar and/or phosphate modifications) or replaced with another base without significant effect. Helix 4 can be formed from two separate molecules, i.e., without a connecting loop. The connecting loop when present may be a ribonucleotide with or without modifications to its base, sugar or phosphate. "q" is ≥ 2 bases. The connecting loop can also be replaced with a non-nucleotide linker molecule. H, refers to bases A, U or C. Y refers to pyrimidine bases.

Figure 4 is a representation of the general structure of the hepatitis delta virus ribozyme domain known in the art.

Figure 5 is a representation of the general structure of the self-cleaving VS RNA ribozyme domain.

Figure 6 is a schematic representation of an RNAseH accessibility assay. Specifically, the left side of Figure 6 is a diagram of complementary DNA oligonucleotides bound to accessible sites on the target RNA. Complementary DNA oligonucleotides are represented by broad lines labeled A, B, and C. Target RNA is represented by the thin, twisted line. The right side of Figure 6 is a schematic of a gel separation of uncut target RNA from a cleaved target RNA. Detection of target RNA is by autoradiography of body-labeled, T7 transcript. The bands common to each lane represent uncleaved target RNA; the bands unique to each lane represent the cleaved products.

Ribozymes

Ribozymes of this invention block to some extent CETP production and can be used to treat disease or diagnose such disease. Ribozymes will be delivered to cells in culture and to cells or tissues in animal models of cardiovascular disorders. Ribozyme cleavage of CETP encoded mRNAs in these systems may alleviate disease symptoms.

Target sites

Targets for useful ribozymes can be determined as disclosed in Draper et al., "Method and reagent for treatment of arthritic conditions U.S.S.N. 08/152,487, filed 11/12/93, and hereby incorporated by reference herein in totality. Rather than repeat the guidance provided in those documents here, below are provided specific examples of such methods, not limiting to those in the art. Ribozymes to such targets are designed as described in those applications and synthesized to be tested in vitro and in vivo, as also described.

The sequence of human and rabbit CETP mRNAs were screened for optimal ribozyme target sites using a computer folding algorithm. Hammerhead or hairpin ribozyme cleavage sites were identified. These sites are

shown in Tables II, IV, VI and VII (All sequences are 5' to 3' in the tables) The nucleotide base position is noted in the Tables as that site to be cleaved by the designated type of ribozyme. While rabbit and human sequences can be screened and ribozymes thereafter designed, the human targeted sequences are of most utility. However, as discussed in Stinchcomb et al., "Method and Composition for Treatment of Restenosis and Cancer Using Ribozymes," filed May 18, 1994, U.S.S.N. 08/245,466, rabbit targeted ribozymes may be useful to test efficacy of action of the ribozyme prior to testing in humans. The nucleotide base position is noted in the Tables as that site to be cleaved by the designated type of ribozyme.

Hammerhead or hairpin ribozymes are designed that could bind and were individually analyzed by computer folding (Jaeger et al., 1989 Proc. Natl. Acad. Sci. USA, 86, 7706) to assess whether the ribozyme sequences fold into the appropriate secondary structure. Those ribozymes with unfavorable intramolecular interactions between the binding arms and the catalytic core are eliminated from consideration. Varying binding arm lengths can be chosen to optimize activity. Generally, at least 5 bases on each arm are able to bind to, or otherwise interact with, the target RNA.

Referring to Figure 6, mRNA were screened for accessible cleavage sites by the method described generally in McSwiggen, US Patent application 07/883,849 filed on May 1, 1992, entitled "Assay for ribozyme target site", hereby incorporated by reference herein. Briefly, DNA oligonucleotides representing potential hammerhead or hairpin ribozyme cleavage sites were synthesized. A polymerase chain reaction is used to generate substrates for T7 RNA polymerase transcription from human and rabbit CETP cDNA clones. Labeled RNA transcripts are synthesized in vitro from the templates. The oligonucleotides and the labeled transcripts are annealed, RNAseH is added and the mixtures are incubated for the designated times at 37°C. Reactions

are stopped and RNA separated on sequencing polyacrylamide gels. The percentage of the substrate cleaved is determined by autoradiographic quantitation using a PhosphorImaging system. From these data, hammerhead or hairpin ribozyme sites are chosen as the most accessible.

Ribozymes of the hammerhead or hairpin motif are designed to anneal to various sites in the mRNA message. The binding arms are complementary to the target site sequences described above. The ribozymes are chemically synthesized. The method of synthesis used follows the procedure for normal RNA synthesis as described in Usman et al., 1987 J. Am. Chem. Soc., 109, 7845 and in Scaringe et al., 1990 Nucleic Acids Res., 18, 5433 and made use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. The average stepwise coupling yields are >98%. Inactive ribozymes are synthesized by substituting a U for G_5 and a U for A_{14} (numbering from Hertel et al., 1992 Nucleic Acids Res., 20, 3252). Hairpin ribozymes are synthesized in two parts and annealed to reconstruct the active ribozyme (Chowrira and Burke, 1992 Nucl. Acids. Res., 20, 2835-2840). Ribozymes are also synthesized from DNA templates using bacteriophage T7 RNA polymerase (Milligan and Uhlenbeck, 1989, Methods Enzymol. 180, 51). All ribozymes are modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-flouro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992 TIBS 17, 34). Ribozymes are purified by gel electrophoresis using general methods or are purified by high pressure liquid chromatography (HPLC; See Usman et al., Synthesis, deprotection, analysis and purification of RNA and ribozymes, filed May, 18, 1994, U.S.S.N. 08/245,736 the totality of which is hereby incorporated herein by reference) and are resuspended in water.

The sequences of the ribozymes that are chemically synthesized, useful in this study, are shown in Tables

III, V, VI and VII. Those in the art will recognize that these sequences are representative only of many more such sequences where the enzymatic portion of the ribozyme (all but the binding arms) is altered to affect activity. For example, stem-loop II sequence of hammerhead ribozymes listed in Tables III and V (5'-GGCCGAAAGGCC-3') can be altered (substitution, deletion, and/or insertion) to contain any sequences provided a minimum of two base-paired stem structure can form. Similarly, stem-loop IV sequence of hairpin ribozymes listed in Tables VI and VII (5'-CACGUUGUG-3') can be altered (substitution, deletion, and/or insertion) to contain any sequence, provided a minimum of two base-paired stem structure can form. The sequences listed in Tables III, V, VI and VII may be formed of ribonucleotides or other nucleotides or non-nucleotides. Such ribozymes are equivalent to the ribozymes described specifically in the Tables.

Optimizing Ribozyme Activity

Ribozyme activity can be optimized as described by Stinchcomb et al., supra. The details will not be repeated here, but include altering the length of the ribozyme binding arms (stems I and III, see Figure 2c), or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see e.g., Eckstein et al., International Publication No. WO 92/07065; Perrault et al., 1990 Nature 344, 565; Pieken et al., 1991 Science 253, 314; Usman and Cedergren, 1992 Trends in Biochem. Sci. 17, 334; Usman et al., International Publication No. WO 93/15187; and Rossi et al., International Publication No. WO 91/03162, as well as Usman, N. et al. US Patent Application 07/829,729, and Sproat, European Patent Application 92110298.4 which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules, modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times

and reduce chemical requirements. (All these publications are hereby incorporated by reference herein.),

Sullivan, et al., supra, describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered ex vivo to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination is locally delivered by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Sullivan et al., supra and Draper et al., supra which have been incorporated by reference herein.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA or RNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990 Proc. Natl. Acad. Sci. USA, 87, 6743-7; Gao and Huang 1993 Nucleic Acids Res.,

21, 2867-72; Lieber et al., 1993 Methods Enzymol., 217, 47-66; Zhou et al., 1990 Mol. Cell. Biol., 10, 4529-37). Several investigators have demonstrated that ribozymes expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet et al., 1992 Antisense Res. Dev., 2, 3-15; Ojwang et al., 1992 Proc. Natl. Acad. Sci. USA, 89, 10802-6; Chen et al., 1992 Nucleic Acids Res., 20, 4581-9; Yu et al., 1993 Proc. Natl. Acad. Sci. USA, 90, 6340-4; L'Huillier et al., 1992 EMBO J. 11, 4411-8; Lisziewicz et al., 1993 Proc. Natl. Acad. Sci. USA, 90, 8000-4). The above ribozyme transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors).

In a preferred embodiment of the invention, a transcription unit expressing a ribozyme that cleaves mRNAs encoded by CETP is inserted into a plasmid DNA vector or an adenovirus or adeno-associated virus DNA viral vector or a retroviral RNA vector. Viral vectors have been used to transfer genes and lead to either transient or long term gene expression (Zabner et al., 1993 Cell 75, 207; Carter, 1992 Curr. Opi. Biotech. 3, 533). The adenovirus vector is delivered as recombinant adenoviral particles. The DNA may be delivered alone or complexed with vehicles (as described for RNA above). The recombinant adenovirus or AAV particles are locally administered to the site of treatment, e.g., through incubation or inhalation in vivo or by direct application to cells or tissues ex vivo.

In another preferred embodiments, the ribozyme is administered to the site of CETP expression (e.g., liver cells) in an appropriate liposomal vesicle.

Example 1: CETP Hammerhead ribozymes

By engineering ribozyme motifs we have designed several ribozymes directed against CETP encoded mRNA

sequences. These ribozymes are synthesized with modifications that improve their nuclease resistance. The ability of ribozymes to cleave target sequences in vitro was evaluated.

Several common human cell lines, such as HepG2, are available that can be induced to express endogenous CETP for experimental purposes. Alternatively, non-human cell lines have been developed which constitutively express a cDNA encoding for human CETP (Wang et al., 1991 Biochemistry 30, 3484; Wang et al., 1992 J. Biol. Chem. 267, 17487). Additional lines expressing human or rabbit full length or exon 9 deleted cDNA under the control of inducible or constitutive promoters could readily be developed by those skilled in the art. Several rabbit animal models of experimental hypercholesterolemia are available. New Zealand white rabbits fed with high cholesterol diets have been shown to develop atherosclerotic disease (Clarkson et al., 1988 in Use of Animal Models For Reasearch in Human Nutrition, Comparative Animal Nutrition vol. 6, Bexnen and West, eds.) and Watanabe rabbits are a model of homozygous FH (defective LDL receptor) and present with increased cholesterol levels and spontaneous development of atherosclerosis and tendinous xanthomas (Watanbe, 1980 Atherosclerosis 36, 261). CETP protein levels can be measured clinically or experimentally by ELISA, or radioimmuno assay. CETP enzyme activity can be measured in vitro or ex vivo by the use of a fluorescently labeled substrate (Bisgaier et al., 1993 J. Lipid Res. 34, 1625; Bisgaier et al., 1994 Lipids 29, in press). CETP encoded mRNA levels can be assessed by Northern analysis, RNAse protection, primer extension analysis or quantitative RT-PCR. Ribozymes that block the induction of CETP activity and/or CETP protein encoding mRNAs by more than 20% in vitro can be identified.

RNA ribozymes and/or genes encoding them will be delivered by either free delivery, liposome delivery, cationic lipid delivery, adeno-associated virus vector

delivery, adenovirus vector delivery, retrovirus vector delivery or plasmid vector delivery in these animal model (e.g., transgenic mouse) experiments. One dose of a ribozyme vector that constitutively expresses the ribozyme or one or more doses of a stable anti-CETP ribozyme or a transiently expressing ribozyme vector may reduce the incidence or severity of atherosclerotic lesions or heart disease.

Diagnostic uses

Ribozymes of this invention may be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of CETP RNA in a cell. The close relationship between ribozyme activity and the structure of the target RNA allows the detection of mutations in any region of the molecule which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple ribozymes described in this invention, one may map nucleotide changes which are important to RNA structure and function in vitro, as well as in cells and tissues. Cleavage of target RNAs with ribozymes may be used to inhibit gene expression and define the role (essentially) of specified gene products in the progression of disease. In this manner, other genetic targets may be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combinational therapies (e.g., multiple ribozymes targeted to different genes, ribozymes coupled with known small molecule inhibitors, or intermittent treatment with combinations of ribozymes and/or other chemical or biological molecules). Other in vitro uses of ribozymes of this invention are well known in the art, and include detection of the presence of mRNAs associated with CETP_related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a ribozyme using standard methodology.

In a specific example, ribozymes which can cleave only wild-type or mutant forms of the target RNA are used for the assay. The first ribozyme is used to identify wild-type RNA present in the sample and the second ribozyme will be used to identify mutant RNA in the sample. As reaction controls, synthetic substrates of both wild-type and mutant RNA will be cleaved by both ribozymes to demonstrate the relative ribozyme efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates will also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus each analysis will require two ribozymes, two substrates and one unknown sample which will be combined into six reactions. The presence of cleavage products will be determined using an RNAse protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (i.e., CETP) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels will be adequate and will decrease the cost of the initial diagnosis. Higher mutant form to wild-type ratios will be correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

Other embodiments are within the following claims.

Table I

Characteristics of Ribozymes

Group I Introns

Size: ~200 to >1000 nucleotides.

Requires a U in the target sequence immediately 5' of the cleavage site.

Binds 4-6 nucleotides at 5'side of cleavage site.

Over 75 known members of this class. Found in Tetrahymena thermophila rRNA, fungal mitochondria, chloroplasts, phage T4, blue-green algae, and others.

RNAseP RNA (M1 RNA)

Size: ~290 to 400 nucleotides.

RNA portion of a ribonucleoprotein enzyme. Cleaves tRNA precursors to form mature tRNA.

Roughly 10 known members of this group all are bacterial in origin.

Hammerhead Ribozyme

Size: ~13 to 40 nucleotides.

Requires the target sequence UH immediately 5' of the cleavage site.

Binds a variable number nucleotides on both sides of the cleavage site.

14 known members of this class. Found in a number of plant pathogens (virusoids) that use RNA as the infectious agent (Figure 1)

Hairpin Ribozyme

Size: ~50 nucleotides.

Requires the target sequence GUC immediately 3' of the cleavage site.

Binds 4-6 nucleotides at 5'side of the cleavage site and a variable number to the 3'side of the cleavage site.

Only 3 known member of this class. Found in three plant pathogen (satellite RNAs of the tobacco ringspot virus, arabis mosaic virus and chicory yellow mottle virus) which uses RNA as the infectious agent (Figure 3).

Hepatitis Delta Virus (HDV) Ribozyme

Size: 50 - 60 nucleotides (at present).

Cleavage of target RNAs recently demonstrated.
Sequence requirements not fully determined.
Binding sites and structural requirements not fully determined, although no sequences 5' of cleavage site are required.
Only 1 known member of this class. Found in human HDV (Figure 4).

Neurospora VS RNA Ribozyme

Size: ~144 nucleotides (at present)
Cleavage of target RNAs recently demonstrated.
Sequence requirements not fully determined.
Binding sites and structural requirements not fully determined. Only 1 known member of this class. Found in Neurospora VS RNA (Figure 5).

Table II: Human CETP HH Target Sequence

nt. Sequence	Target Sequence	nt. Sequence	Target Sequence
9	UGAAUCU C UGGGGCC	440	CUCCAUU C AGAACGU
45	AGAGCCU C AUGUUCC	450	AACGUGU C UGUGGUC
50	CUCAUGU U CCGUGGG	457	CUGUGGU C UUCAAGG
51	UCAUGUU C CGUGGGG	459	GUGGUCU U CAAGGGG
72	CGGACAU A CAUAUAC	460	UGGUCUU C AAGGGGA
76	CAUACAU A UACGGGC	477	CUGAAGU A UGGCUAC
78	UACAUAU A CGGGCUC	483	UAUGGCU A CACCACU
85	ACGGGCU C CAGGCUG	506	GCUGGGU A UUGAUCA
100	AACGGCU C GGGCCAC	508	UGGGUAU U GAUCAGU
109	GGCCACU U ACACACC	512	UAUUGAU C AGUCCAU
110	GCCACUU A CACACCA	516	GAUCAGU C CAUUGAC
127	GCCUGAU A ACCAUGC	520	AGUCCAU U GACUUCG
148	CCACAGU C CUGACCC	525	AUUGACU U CGAGAUC
186	GCCUGCU C CAAAGGC	526	UUGACUU C GAGAUCG
198	GGCACCU C GCACGAG	532	UCGAGAU C GACUCUG
214	CAGGCAU C GUGUGCC	537	AUCGACU C UGCCAUU
226	GCCGCAU C ACCAAGC	544	CUGCCAU U GACCUCC
241	CUGCCCU C CUGGUGU	550	UUGACCU C CAGAUCA
249	CUGGUGU U GAACCAC	556	UCCAGAU C AACACAC

	274	AGGUGAU C CAGACCG	579	UGUGACU C UGGUAGA
	285	ACCGCCU U CCAGCGA	584	CUCUGGU A GAGUGCG
	286	CCGCCUU C CAGCGAG	612	GACUGCU A CCUGUCU
	300	GCCAGCU A CCCAGAU	618	UACCUGU C UUUCCAU
5	308	CCCAGAU A UCACGGG	620	CCUGUCU U UCCAUAA
	310	CAGAUAU C ACGGGCG	621	CUGUCUU U CCAUAAG
	334	UGAUGCU C CUUGGCC	622	UGUCUUU C CAUAAGC
	337	UGCUCCU U GGCCAAG	626	UUUCCAU A AGCUGCU
	346	GCCAAGU C AAGUAUG	634	AGCUGCU C CUGCAUC
10	351	GUCAAGU A UGGGUUG	641	CCUGCAU C UCCAAGG
	357	UAUGGGU U GCACAAC	643	UGCAUCU C CAAGGGG
	367	ACAACAU C CAGAUCA	670	GGUGGAU C AAGCAGC
	373	UCCAGAU C AGCCACU	681	CAGCUGU U CACAAAU
	381	AGCCACU U GUCCAUC	682	AGCUGUU C ACAAAUU
15	384	CACUUGU C CAUCGCC	689	CACAAAU U UCAUCUC
	388	UGUCCAU C GCCAGCA	690	ACAAAUU U CAUCUCC
	423	GCCAAGU C CAUUGAU	691	CAAAUUU C AUCUCCU
	427	AGUCCAU U GAUGUCU	694	AUUUCAU C UCCUUCA
	433	UUGAUGU C UCCAUUC	696	UUCAUCU C CUUCACC
20	435	GAUGUCU C CAUUCAG	699	AUCUCCU U CACCCUG
	439	UCUCCAU U CAGAACG	700	UCUCCUU C ACCCUGA
	715	AGCUGGU C CUGAAGG	991	GAGUCUU C CACUCGC
	730	GACAGAU C UGCAAAG	996	UUCCACU C GCUGGCC
	742	AAGAGAU C AACGUCA	1009	CCAAGGU A GCUUUCC
25	748	UCAACGU C AUCUCUA	1013	GGUAGCU U UCCAGGA
	751	ACGUCAU C UCUAACA	1014	GUAGCUU U CCAGGAU
	753	GUCAUCU C UAACAUC	1015	UAGCUUU C CAGGAUG
	755	CAUCUCU A ACAUCAU	1030	GCCGCCU C AUGCUCA
	760	CUAACAU C AUGGCCG	1036	UCAUGCU C AGCCUGA
30	770	GGCCGAU U UUGUCCA	1056	GACGAGU U CAAGGCA
	771	GCCGAUU U UGUCCAG	1057	ACGAGUU C AAGGCAG
	772	CCGAUUU U GUCCAGA	1083	UGGGGCU U CAACACC
	775	AUUUUGU C CAGACAA	1084	GGGGCUU C AACACCA
	796	CCAGCAU C CUUUCAG	1102	AGGAAAU C UUCCAAG
35	799	GCAUCCU U UCAGAUG	1104	GAAAUCU U CCAAGAG
	800	CAUCCUU U CAGAUGG	1105	AAAUCUU C CAAGAGG
	801	AUCCUUU C AGAUGGA	1114	AAGAGGU U GUCGGCG

	814	GAGACAU U GGGGUGG	1117	AGGUUGU C GGCGGCU
	826	UGGACAU U UCCCUGA	1125	GGCGGCU U CCCCAGC
	827	GGACAUU U CCCUGAC	1126	GCGGCUU C CCCAGCC
	828	GACAUUU C CCUGACA	1144	CCCAAGU C ACCGUCC
5	842	AGGUGAU C CCGUCAU	1150	UCACCGU C CACUGCC
	847	AUCCCGU C AUCACAG	1159	ACUGCCU C AAGAUGC
	850	CCGUCAU C ACAGCCU	1174	CCAAGAU C UCCUGCC
	858	ACAGCCU C CUACCUG	1176	AAGAUCU C CUGCCAA
	861	GCCUCCU A CCUGGAG	1195	AGGGAGU C GUGGUCA
10	870	CUGGAGU C CCAUCAC	1201	UCGUGGU C AAUUCUU
	875	GUCCCAU C ACAAGGG	1205	GGUCAAU U CUUCAGU
	884	CAAGGGU C AUUUCAU	1206	GUCAAUU C UUCAGUG
	887	GGGUCAU U UCAUCUA	1208	CAAUUCU U CAGUGAU
	888	GGUCAUU U CAUCUAC	1209	AAUUCUU C AGUGAUG
15	889	GUCAUUU C AUCUACA	1224	GUGAAAU U CCUCUUU
	892	AUUUCAU C UACAAGA	1225	UGAAAUU C CUCUUUC
	894	UUCAUCU A CAAGAAU	1228	AAUUCCU C UUUCCAC
	904	AGAAUGU C UCAGAGG	1230	UUCCUCU U UCCACGC
	906	AAUGUCU C AGAGGAC	1231	UCCUCUU U CCACGCC
20	916	AGGACCU C CCCCUCC	1232	CCUCUUU C CACGCCC
	922	UCCCCCU C CCCACCU	1253	GCAACAU U CUGUAGC
	930	CCCACCU U CUCGCCC	1254	CAACAUU C UGUAGCU
	931	CCACCUU C UCGCCCA	1258	AUUCUGU A GCUUACA
	933	ACCUUCU C GCCCACA	1262	UGUAGCU U ACACAUU
25	954	GGGGACU C CCGCAUG	1263	GUAGCUU A CACAUUU
	966	AUGCUGU A CUUCUGG	1269	UACACAU U UGAAGAG
	969	CUGUACU U CUGGUUC	1270	ACACAUU U GAAGAGG
	970	UGUACUU C UGGUUCU	1280	AGAGGAU A UCGUGAC
	975	UUCUGGU U CUCUGAG	1282	AGGAUAU C GUGACUA
30	976	UCUGGUU C UCUGAGC	1289	CGUGACU A CCGUCCA
	978	UGGUUCU C UGAGCGA	1294	CUACCGU C CAGGCCU
	988	AGCGAGU C UUCCACU	1302	CAGGCCU C CUAUUCU
	990	CGAGUCU U CCACUCG	1305	GCCUCCU A UUCUAAG
	1307	CUCCUAU U CUAAGAA	1569	UUUGGCU U CCCUGAG
35	1308	UCCUAUU C UAAGAAA	1570	UUGGCUU C CCUGAGC
	1310	CUAUUCU A AGAAAAA	1592	GGUGGAU U UCCUCCA
	1321	AAAAGCU C UUCUUAA	1593	GUGGAUU U CCUCCAG

1323	AAGCUCU	U CUUAAGC	1594	UGGAUUU	C CUCCAGA
1324	AGCUCUU	C UUAAGCC	1597	AUUUCCU	C CAGAGCU
1326	CUCUUCU	U AAGCCUC	1605	CAGAGCU	U GAGCUAG
1327	UCUUCUU	A AGCCUCU	1611	UUGAGCU	A GAAGUCU
1333	UAAGCCU	C UUGGAUU	1617	UAGAAGU	C UCCAAGG
1335	AGCCUCU	U GGAUUUC	1619	GAAGUCU	C CAAGGAG
1340	CUUGGAU	U UCCAGAU	1629	AGGAGGU	C GGGAUGG
1341	UUGGAUU	U CCAGAUU	1641	UGGGGCU	U GUAGCAG
1342	UGGAUUU	C CAGAUUA	1644	GGCUUGU	A GCAGAAG
1348	UCCAGAU	U ACACCAA	1666	CCAGGCU	C ACAGCUG
1349	CCAGAUU	A CACCAAA	1686	CUGGUGU	C UCCUCCA
1363	AGACUGU	U UCCAACU	1688	GGUGUCU	C CUCCAGC
1364	GACUGUU	U CCAACUU	1691	GUCUCCU	C CAGCGUG
1365	ACUGUUU	C CAACUUG	1707	UGGAAGU	U GGGUUAG
1371	UCCAACU	U GACUGAG	1712	GUUGGGU	U AGGAGUA
1386	AGCAGCU	C CGAGUCC	1713	UUGGGUU	A GGAGUAC
1392	UCCGAGU	C CAUCCAG	1719	UAGGAGU	A CGGAGAU
1396	AGUCCAU	C CAGAGCU	1733	UGGAGAU	U GGCUCCC
1404	CAGAGCU	U CCUGCAG	1738	AUUGGCU	C CCAACUC
1405	AGAGCUU	C CUGCAGU	1745	CCCAACU	C CUCCCUA
1413	CUGCAGU	C AAUGAUC	1748	AACUCCU	C CCUAUCC
1420	CAAUGAU	C ACCGCUG	1752	CCUCCCU	A UCCUAAA
1435	UGGGCAU	C CCUGAGG	1754	UCCCUAU	C CUAAAGG
1444	CUGAGGU	C AUGUCUC	1757	CUAUCCU	A AAGGCCC
1449	GUCAUGU	C UCGGCUC	1773	CUGGCAU	U AAAGUGC
1451	CAUGUCU	C GGCUCGA	1774	UGGCAUU	A AAGUGCU
1462	UCGAGGU	A GUGUUUA			
1467	GUAGUGU	U UACAGCC			
1468	UAGUGUU	U ACAGCCC			
1469	AGUGUUU	A CAGCCCU			
1477	CAGCCCU	C AUGAACA			
1501	UGAGCCU	C UUCGACA			
1503	AGCCUCU	U CGACAUC			
1504	GCCUCUU	C GACAUCA			
1510	UCGACAU	C AUCAACC			
1513	ACAUCAU	C AACCCUG			
1525	CUGAGAU	U AUCACUC			

1526	UGAGAUU	A UCACUCG
1528	AGAUUAU	C ACUCGAG
1532	UAUCACU	C GAGAUGG
1542	GAUGGCU	U CCUGCUG
1543	AUGGCUU	C CUGCUGC
1563	AUGGACU	U UGGCUUC
1564	UGGACUU	U GGCUUCC

Table III: Human CETP HH Ribozyme Sequence

nt. Position	HH Ribozyme Sequence
9	GGCCCCA CUGAUGAGGCCGAAAGGCCGAA AGAUUCA
45	GGAACAU CUGAUGAGGCCGAAAGGCCGAA AGGCUCU
50	CCCACGG CUGAUGAGGCCGAAAGGCCGAA ACAUGAG
51	CCCCACG CUGAUGAGGCCGAAAGGCCGAA AACAUGA
72	GUAUAUG CUGAUGAGGCCGAAAGGCCGAA AUGUCCG
76	GCCCGUA CUGAUGAGGCCGAAAGGCCGAA AUGUAUG
78	GAGCCCG CUGAUGAGGCCGAAAGGCCGAA AUAUGUA
85	CAGCCUG CUGAUGAGGCCGAAAGGCCGAA AGCCCGU
100	GUGGCCC CUGAUGAGGCCGAAAGGCCGAA AGCCGUU
109	GGUGUGU CUGAUGAGGCCGAAAGGCCGAA AGUGGCC
110	UGGUGUG CUGAUGAGGCCGAAAGGCCGAA AAGUGGC
127	GCAUGGU CUGAUGAGGCCGAAAGGCCGAA AUCAGGC
148	GGGUCAG CUGAUGAGGCCGAAAGGCCGAA ACUGUGG
186	GCCUUUG CUGAUGAGGCCGAAAGGCCGAA AGCAGGC
198	CUCGUGC CUGAUGAGGCCGAAAGGCCGAA AGGUGCC
214	GGCACAC CUGAUGAGGCCGAAAGGCCGAA AUGCCUG
226	GCUUGGU CUGAUGAGGCCGAAAGGCCGAA AUGCGGC
241	ACACCAG CUGAUGAGGCCGAAAGGCCGAA AGGGCAG
249	GUGGUUC CUGAUGAGGCCGAAAGGCCGAA ACACCAG
274	CGGUCUG CUGAUGAGGCCGAAAGGCCGAA AUCACCU
285	UCGCUGG CUGAUGAGGCCGAAAGGCCGAA AGGCGGU
286	CUCGCUG CUGAUGAGGCCGAAAGGCCGAA AAGGCGG
300	AUCUGGG CUGAUGAGGCCGAAAGGCCGAA AGCUGGC
308	CCCGUGA CUGAUGAGGCCGAAAGGCCGAA AUCUGGG
310	CGCCCGU CUGAUGAGGCCGAAAGGCCGAA AUAUCUG
334	GGCCAAG CUGAUGAGGCCGAAAGGCCGAA AGCAUCA

337	CUUGGCC	CUGAUGAGGCCGAAAGGCCGAA AGGAGCA
346	CAUACUU	CUGAUGAGGCCGAAAGGCCGAA ACUUGGC
351	CAACCCA	CUGAUGAGGCCGAAAGGCCGAA ACUUGAC
357	GUUGUGC	CUGAUGAGGCCGAAAGGCCGAA ACCCAUA
367	UGAUCUG	CUGAUGAGGCCGAAAGGCCGAA AUGUUGU
373	AGUGGCU	CUGAUGAGGCCGAAAGGCCGAA AUCUGGA
381	GAUGGAC	CUGAUGAGGCCGAAAGGCCGAA AGUGGCU
384	GGCGAUG	CUGAUGAGGCCGAAAGGCCGAA ACAAGUG
388	UGCUGGC	CUGAUGAGGCCGAAAGGCCGAA AUGGACA
423	AUCAAUG	CUGAUGAGGCCGAAAGGCCGAA ACUUGGC
427	AGACAUC	CUGAUGAGGCCGAAAGGCCGAA AUGGACU
433	GAAUGGA	CUGAUGAGGCCGAAAGGCCGAA ACAUCAA
435	CUGAAUG	CUGAUGAGGCCGAAAGGCCGAA AGACAUC
439	CGUUCUG	CUGAUGAGGCCGAAAGGCCGAA AUGGAGA
440	ACGUUCU	CUGAUGAGGCCGAAAGGCCGAA AAUGGAG
450	GACCACA	CUGAUGAGGCCGAAAGGCCGAA ACACGUU
457	CCUUGAA	CUGAUGAGGCCGAAAGGCCGAA ACCACAG
459	CCCCUUG	CUGAUGAGGCCGAAAGGCCGAA AGACCAC
460	UCCCCUU	CUGAUGAGGCCGAAAGGCCGAA AAGACCA
477	GUAGCCA	CUGAUGAGGCCGAAAGGCCGAA ACUUCAG
483	AGUGGUG	CUGAUGAGGCCGAAAGGCCGAA AGCCAUA
506	UGAUCAA	CUGAUGAGGCCGAAAGGCCGAA ACCCAGC
508	ACUGAUC	CUGAUGAGGCCGAAAGGCCGAA AUACCCA
512	AUGGACU	CUGAUGAGGCCGAAAGGCCGAA AUCAAUA
516	GUCAAUG	CUGAUGAGGCCGAAAGGCCGAA ACUGAUC
520	CGAAGUC	CUGAUGAGGCCGAAAGGCCGAA AUGGACU
525	GAUCUCG	CUGAUGAGGCCGAAAGGCCGAA AGUCAAU
526	CGAUCUC	CUGAUGAGGCCGAAAGGCCGAA AAGUCAA
532	CAGAGUC	CUGAUGAGGCCGAAAGGCCGAA AUCUCGA
537	AAUGGCA	CUGAUGAGGCCGAAAGGCCGAA AGUCGAU
544	GGAGGUC	CUGAUGAGGCCGAAAGGCCGAA AUGGCAG
550	UGAUCUG	CUGAUGAGGCCGAAAGGCCGAA AGGUCAA
556	GUGUGUU	CUGAUGAGGCCGAAAGGCCGAA AUCUGGA
579	UCUACCA	CUGAUGAGGCCGAAAGGCCGAA AGUCACA
584	CGCACUC	CUGAUGAGGCCGAAAGGCCGAA ACCAGAG
612	AGACAGG	CUGAUGAGGCCGAAAGGCCGAA AGCAGUC
618	AUGGAAA	CUGAUGAGGCCGAAAGGCCGAA ACAGGUA

620	UUAUGGA	CUGAUGAGGCCGAAAGGCCGAA AGACAGG
621	CUUAUGG	CUGAUGAGGCCGAAAGGCCGAA AAGACAG
622	GCUUAUG	CUGAUGAGGCCGAAAGGCCGAA AAAGACA
626	AGCAGCU	CUGAUGAGGCCGAAAGGCCGAA AUGGAAA
634	GAUGCAG	CUGAUGAGGCCGAAAGGCCGAA AGCAGCU
641	CCUUGGA	CUGAUGAGGCCGAAAGGCCGAA AUGCAGG
643	CCCCUUG	CUGAUGAGGCCGAAAGGCCGAA AGAUGCA
670	GCUGCUU	CUGAUGAGGCCGAAAGGCCGAA AUCCACC
681	AUUUGUG	CUGAUGAGGCCGAAAGGCCGAA ACAGCUG
682	AAUUUGU	CUGAUGAGGCCGAAAGGCCGAA AACAGCU
689	GAGAUGA	CUGAUGAGGCCGAAAGGCCGAA AUUUGUG
690	GGAGAUG	CUGAUGAGGCCGAAAGGCCGAA AAUUUGU
691	AGGAGAU	CUGAUGAGGCCGAAAGGCCGAA AAAUUUG
694	UGAAGGA	CUGAUGAGGCCGAAAGGCCGAA AUGAAAU
696	GGUGAAG	CUGAUGAGGCCGAAAGGCCGAA AGAUGAA
699	CAGGGUG	CUGAUGAGGCCGAAAGGCCGAA AGGAGAU
700	UCAGGGU	CUGAUGAGGCCGAAAGGCCGAA AAGGAGA
715	CCUUCAG	CUGAUGAGGCCGAAAGGCCGAA ACCAGCU
730	CUUUGCA	CUGAUGAGGCCGAAAGGCCGAA AUCUGUC
742	UGACGUU	CUGAUGAGGCCGAAAGGCCGAA AUCUCUU
748	UAGAGAU	CUGAUGAGGCCGAAAGGCCGAA ACGUUGA
751	UGUUAGA	CUGAUGAGGCCGAAAGGCCGAA AUGACGU
753	GAUGUUA	CUGAUGAGGCCGAAAGGCCGAA AGAUGAC
755	AUGAUGU	CUGAUGAGGCCGAAAGGCCGAA AGAGAUG
760	CGGCCAU	CUGAUGAGGCCGAAAGGCCGAA AUGUUAG
770	UGGACAA	CUGAUGAGGCCGAAAGGCCGAA AUCGGCC
771	CUGGACA	CUGAUGAGGCCGAAAGGCCGAA AAUCGGC
772	UCUGGAC	CUGAUGAGGCCGAAAGGCCGAA AAAUCGG
775	UUGUCUG	CUGAUGAGGCCGAAAGGCCGAA ACAAAAU
796	CUGAAAG	CUGAUGAGGCCGAAAGGCCGAA AUGCUGG
799	CAUCUGA	CUGAUGAGGCCGAAAGGCCGAA AGGAUGC
800	CCAUCUG	CUGAUGAGGCCGAAAGGCCGAA AAGGAUG
801	UCCAUCU	CUGAUGAGGCCGAAAGGCCGAA AAAGGAU
814	CCACCCC	CUGAUGAGGCCGAAAGGCCGAA AUGUCUC
826	UCAGGGA	CUGAUGAGGCCGAAAGGCCGAA AUGUCCA
827	GUCAGGG	CUGAUGAGGCCGAAAGGCCGAA AAUGUCC
828	UGUCAGG	CUGAUGAGGCCGAAAGGCCGAA AAAUGUC

842	AUGACGG	CUGAUGAGGCCGAAAGGCCGAA AUCACCU
847	CUGUGAU	CUGAUGAGGCCGAAAGGCCGAA ACGGGAU
850	AGGCUGU	CUGAUGAGGCCGAAAGGCCGAA AUGACGG
858	CAGGUAG	CUGAUGAGGCCGAAAGGCCGAA AGGCUGU
861	CUCCAGG	CUGAUGAGGCCGAAAGGCCGAA AGGAGGC
870	GUGAUGG	CUGAUGAGGCCGAAAGGCCGAA ACUCCAG
875	CCCUUGU	CUGAUGAGGCCGAAAGGCCGAA AUGGGAC
884	AUGAAAU	CUGAUGAGGCCGAAAGGCCGAA ACCCUUG
887	UAGAUGA	CUGAUGAGGCCGAAAGGCCGAA AUGACCC
888	GUAGAUG	CUGAUGAGGCCGAAAGGCCGAA AAUGACC
889	UGUAGAU	CUGAUGAGGCCGAAAGGCCGAA AAAUGAC
892	UCUUGUA	CUGAUGAGGCCGAAAGGCCGAA AUGAAAU
894	AUUCUUG	CUGAUGAGGCCGAAAGGCCGAA AGAUGAA
904	CCUCUGA	CUGAUGAGGCCGAAAGGCCGAA ACAUUCU
906	GUCCUCU	CUGAUGAGGCCGAAAGGCCGAA AGACAUU
916	GGAGGGG	CUGAUGAGGCCGAAAGGCCGAA AGGUCCU
922	AGGUGGG	CUGAUGAGGCCGAAAGGCCGAA AGGGGGA
930	GGGCGAG	CUGAUGAGGCCGAAAGGCCGAA AGGUGGG
931	UGGGCGA	CUGAUGAGGCCGAAAGGCCGAA AAGGUGG
933	UGUGGGC	CUGAUGAGGCCGAAAGGCCGAA AGAAGGU
954	CAUGCGG	CUGAUGAGGCCGAAAGGCCGAA AGUCCCC
966	CCAGAAG	CUGAUGAGGCCGAAAGGCCGAA ACAGCAU
969	GAACCAG	CUGAUGAGGCCGAAAGGCCGAA AGUACAG
970	AGAACCA	CUGAUGAGGCCGAAAGGCCGAA AAGUACA
975	CUCAGAG	CUGAUGAGGCCGAAAGGCCGAA ACCAGAA
976	GCUCAGA	CUGAUGAGGCCGAAAGGCCGAA AACCAGA
978	UCGCUCA	CUGAUGAGGCCGAAAGGCCGAA AGAACCA
988	AGUGGAA	CUGAUGAGGCCGAAAGGCCGAA ACUCGCU
990	CGAGUGG	CUGAUGAGGCCGAAAGGCCGAA AGACUCG
991	GCGAGUG	CUGAUGAGGCCGAAAGGCCGAA AAGACUC
996	GGCCAGC	CUGAUGAGGCCGAAAGGCCGAA AGUGGAA
1009	GGAAAGC	CUGAUGAGGCCGAAAGGCCGAA ACCUUGG
1013	UCCUGGA	CUGAUGAGGCCGAAAGGCCGAA AGCUACC
1014	AUCCUGG	CUGAUGAGGCCGAAAGGCCGAA AAGCUAC
1015	CAUCCUG	CUGAUGAGGCCGAAAGGCCGAA AAAGCUA
1030	UGAGCAU	CUGAUGAGGCCGAAAGGCCGAA AGGCGGC
1036	UCAGGCU	CUGAUGAGGCCGAAAGGCCGAA AGCAUGA

	1056	UGCCUUG CUGAUGAGGCCGAAAGGCCGAA ACUCGUC
	1057	CUGCCUU CUGAUGAGGCCGAAAGGCCGAA AACUCGU
	1083	GGUGUUG CUGAUGAGGCCGAAAGGCCGAA AGCCCCA
	1084	UGGUGUU CUGAUGAGGCCGAAAGGCCGAA AAGCCCC
5	1102	CUUGGAA CUGAUGAGGCCGAAAGGCCGAA AUUUCCU
	1104	CUCUUGG CUGAUGAGGCCGAAAGGCCGAA AGAUUUC
	1105	CCUCUUG CUGAUGAGGCCGAAAGGCCGAA AAGAUUU
	1114	CGCCGAC CUGAUGAGGCCGAAAGGCCGAA ACCUCUU
	1117	AGCCGCC CUGAUGAGGCCGAAAGGCCGAA ACAACCU
10	1125	GCUGGGG CUGAUGAGGCCGAAAGGCCGAA AGCCGCC
	1126	GGCUGGG CUGAUGAGGCCGAAAGGCCGAA AAGCCGC
	1144	GGACGGU CUGAUGAGGCCGAAAGGCCGAA ACUUGGG
	1150	GGCAGUG CUGAUGAGGCCGAAAGGCCGAA ACGGUGA
	1159	GCAUCUU CUGAUGAGGCCGAAAGGCCGAA AGGCAGU
15	1174	GGCAGGA CUGAUGAGGCCGAAAGGCCGAA AUCUUGG
	1176	UUGGCAG CUGAUGAGGCCGAAAGGCCGAA AGAUCUU
	1195	UGACCAC CUGAUGAGGCCGAAAGGCCGAA ACUCCCU
	1201	AAGAAUU CUGAUGAGGCCGAAAGGCCGAA ACCACGA
	1205	ACUGAAG CUGAUGAGGCCGAAAGGCCGAA AUUGACC
20	1206	CACUGAA CUGAUGAGGCCGAAAGGCCGAA AAUUGAC
	1208	AUCACUG CUGAUGAGGCCGAAAGGCCGAA AGAAUUG
	1209	CAUCACU CUGAUGAGGCCGAAAGGCCGAA AAGAAUU
	1224	AAAGAGG CUGAUGAGGCCGAAAGGCCGAA AUUUCAC
	1225	GAAAGAG CUGAUGAGGCCGAAAGGCCGAA AAUUUCA
25	1228	GUGGAAA CUGAUGAGGCCGAAAGGCCGAA AGGAAUU
	1230	GCGUGGA CUGAUGAGGCCGAAAGGCCGAA AGAGGAA
	1231	GGCGUGG CUGAUGAGGCCGAAAGGCCGAA AAGAGGA
	1232	GGGCGUG CUGAUGAGGCCGAAAGGCCGAA AAAGAGG
	1253	GCUACAG CUGAUGAGGCCGAAAGGCCGAA AUGUUGC
30	1254	AGCUACA CUGAUGAGGCCGAAAGGCCGAA AAUGUUG
	1258	UGUAAGC CUGAUGAGGCCGAAAGGCCGAA ACAGAAU
	1262	AAUGUGU CUGAUGAGGCCGAAAGGCCGAA AGCUACA
	1263	AAAUGUG CUGAUGAGGCCGAAAGGCCGAA AAGCUAC
	1269	CUCUUCA CUGAUGAGGCCGAAAGGCCGAA AUGUGUA
35	1270	CCUCUUC CUGAUGAGGCCGAAAGGCCGAA AAUGUGU
	1280	GUCACGA CUGAUGAGGCCGAAAGGCCGAA AUCCUCU
	1282	UAGUCAC CUGAUGAGGCCGAAAGGCCGAA AUAUCCU

1289	UGGACGG	CUGAUGAGGCCGAAAGGCCGAA AGUCACG
1294	AGGCCUG	CUGAUGAGGCCGAAAGGCCGAA ACGGUAG
1302	AGAAUAG	CUGAUGAGGCCGAAAGGCCGAA AGGCCUG
1305	CUUAGAA	CUGAUGAGGCCGAAAGGCCGAA AGGAGGC
1307	UUCUUAG	CUGAUGAGGCCGAAAGGCCGAA AUAGGAG
1308	UUUCUUA	CUGAUGAGGCCGAAAGGCCGAA AAUAGGA
1310	UUUUUCU	CUGAUGAGGCCGAAAGGCCGAA AGAAUAG
1321	UUAAGAA	CUGAUGAGGCCGAAAGGCCGAA AGCUUUU
1323	GCUUAAG	CUGAUGAGGCCGAAAGGCCGAA AGAGCUU
1324	GGCUUAA	CUGAUGAGGCCGAAAGGCCGAA AAGAGCU
1326	GAGGCUU	CUGAUGAGGCCGAAAGGCCGAA AGAAGAG
1327	AGAGGCU	CUGAUGAGGCCGAAAGGCCGAA AAGAAGA
1333	AAUCCAA	CUGAUGAGGCCGAAAGGCCGAA AGGCUUA
1335	GAAAUCC	CUGAUGAGGCCGAAAGGCCGAA AGAGGCU
1340	AUCUGGA	CUGAUGAGGCCGAAAGGCCGAA AUCCAAG
1341	AAUCUGG	CUGAUGAGGCCGAAAGGCCGAA AAUCCAA
1342	UAAUCUG	CUGAUGAGGCCGAAAGGCCGAA AAAUCCA
1348	UUGGUGU	CUGAUGAGGCCGAAAGGCCGAA AUCUGGA
1349	UUUGGUG	CUGAUGAGGCCGAAAGGCCGAA AAUCUGG
1363	AGUUGGA	CUGAUGAGGCCGAAAGGCCGAA ACAGUCU
1364	AAGUUGG	CUGAUGAGGCCGAAAGGCCGAA AACAGUC
1365	CAAGUUG	CUGAUGAGGCCGAAAGGCCGAA AAACAGU
1371	CUCAGUC	CUGAUGAGGCCGAAAGGCCGAA AGUUGGA
1386	GGACUCG	CUGAUGAGGCCGAAAGGCCGAA AGCUGCU
1392	CUGGAUG	CUGAUGAGGCCGAAAGGCCGAA ACUCGGA
1396	AGCUCUG	CUGAUGAGGCCGAAAGGCCGAA AUGGACU
1404	CUGCAGG	CUGAUGAGGCCGAAAGGCCGAA AGCUCUG
1405	ACUGCAG	CUGAUGAGGCCGAAAGGCCGAA AAGCUCU
1413	GAUCAUU	CUGAUGAGGCCGAAAGGCCGAA ACUGCAG
1420	CAGCGGU	CUGAUGAGGCCGAAAGGCCGAA AUCAUUG
1435	CCUCAGG	CUGAUGAGGCCGAAAGGCCGAA AUGCCCA
1444	GAGACAU	CUGAUGAGGCCGAAAGGCCGAA ACCUCAG
1449	GAGCCGA	CUGAUGAGGCCGAAAGGCCGAA ACAUGAC
1451	UCGAGCC	CUGAUGAGGCCGAAAGGCCGAA AGACAUG
1456	CUACCUC	CUGAUGAGGCCGAAAGGCCGAA AGCCGAG
1462	UAAACAC	CUGAUGAGGCCGAAAGGCCGAA ACCUCGA
1467	GGCUGUA	CUGAUGAGGCCGAAAGGCCGAA ACACUAC

1468	GGGCUGU	CUGAUGAGGCCGAAAGGCCGAA AACACUA
1469	AGGGCUG	CUGAUGAGGCCGAAAGGCCGAA AAACACU
1477	UGUUCAU	CUGAUGAGGCCGAAAGGCCGAA AGGGCUG
1501	UGUCGAA	CUGAUGAGGCCGAAAGGCCGAA AGGCUCA
1503	GAUGUCG	CUGAUGAGGCCGAAAGGCCGAA AGAGGCU
1504	UGAUGUC	CUGAUGAGGCCGAAAGGCCGAA AAGAGGC
1510	GGUUGAU	CUGAUGAGGCCGAAAGGCCGAA AUGUCGA
1513	CAGGGUU	CUGAUGAGGCCGAAAGGCCGAA AUGAUGU
1525	GAGUGAU	CUGAUGAGGCCGAAAGGCCGAA AUCUCAG
1526	CGAGUGA	CUGAUGAGGCCGAAAGGCCGAA AAUCUCA
1528	CUCGAGU	CUGAUGAGGCCGAAAGGCCGAA AUAAUCU
1532	CCAUCUC	CUGAUGAGGCCGAAAGGCCGAA AGUGAUA
1542	CAGCAGG	CUGAUGAGGCCGAAAGGCCGAA AGCCAUC
1543	GCAGCAG	CUGAUGAGGCCGAAAGGCCGAA AAGCCAU
1563	GAAGCCA	CUGAUGAGGCCGAAAGGCCGAA AGUCCAU
1564	GGAAGCC	CUGAUGAGGCCGAAAGGCCGAA AAGUCCA
1569	CUCAGGG	CUGAUGAGGCCGAAAGGCCGAA AGCCAAA
1570	GCUCAGG	CUGAUGAGGCCGAAAGGCCGAA AAGCCAA
1592	UGGAGGA	CUGAUGAGGCCGAAAGGCCGAA AUCCACC
1593	CUGGAGG	CUGAUGAGGCCGAAAGGCCGAA AAUCCAC
1594	UCUGGAG	CUGAUGAGGCCGAAAGGCCGAA AAAUCCA
1597	AGCUCUG	CUGAUGAGGCCGAAAGGCCGAA AGGAAAU
1605	CUAGCUC	CUGAUGAGGCCGAAAGGCCGAA AGCUCUG
1611	AGACUUC	CUGAUGAGGCCGAAAGGCCGAA AGCUCAA
1617	CCUUGGA	CUGAUGAGGCCGAAAGGCCGAA ACUUCUA
1619	CUCCUUG	CUGAUGAGGCCGAAAGGCCGAA AGACUUC
1629	CCAUCCC	CUGAUGAGGCCGAAAGGCCGAA ACCUCCU
1641	CUGCUAC	CUGAUGAGGCCGAAAGGCCGAA AGCCCCA
1644	CUUCUGC	CUGAUGAGGCCGAAAGGCCGAA ACAAGCC
1666	CAGCUGU	CUGAUGAGGCCGAAAGGCCGAA AGCCUGG
1686	UGGAGGA	CUGAUGAGGCCGAAAGGCCGAA ACACCAG
1688	GCUGGAG	CUGAUGAGGCCGAAAGGCCGAA AGACACC
1691	CACGCUG	CUGAUGAGGCCGAAAGGCCGAA AGGAGAC
1707	CUAACCC	CUGAUGAGGCCGAAAGGCCGAA ACUUCCA
1712	UACUCCU	CUGAUGAGGCCGAAAGGCCGAA ACCCAAC
1713	GUACUCC	CUGAUGAGGCCGAAAGGCCGAA AACCCAA
1719	AUCUCCG	CUGAUGAGGCCGAAAGGCCGAA ACUCCUA

1733	GGGAGCC	CUGAUGAGGCCGAAAGGCCGAA AUCUCCA
1738	GAGUUGG	CUGAUGAGGCCGAAAGGCCGAA AGCCAAU
1745	UAGGGAG	CUGAUGAGGCCGAAAGGCCGAA AGUUGGG
1748	GGAUAGG	CUGAUGAGGCCGAAAGGCCGAA AGGAGUU
1752	UUUAGGA	CUGAUGAGGCCGAAAGGCCGAA AGGGAGG
1754	CCUUUAG	CUGAUGAGGCCGAAAGGCCGAA AUAGGGA
1757	GGGCCUU	CUGAUGAGGCCGAAAGGCCGAA AGGAUAG
1773	GCACUUU	CUGAUGAGGCCGAAAGGCCGAA AUGCCAG
1774	AGCACUU	CUGAUGAGGCCGAAAGGCCGAA AAUGCCA

Table IV: Rabbit CETP HH Target Sequence

nt. Position	Target Sequence	nt. Position	Target Sequence
20	GGCgCCU C cuACGAG	305	uAcAgcU A cACGaGu
23	GCCUcCU a CgAgGcu	305	UAcaGCU A CACgAgU
23	gccUCCU a CgagGCU	305	UaCAgCU A CAcGAgU
36	CuGGCAU C GUGUGuC	323	UGGggGU U GGGcauc
43	cgUGuGU c GCAucAC	330	UGGGcAU c aAUCAGU
43	CgUgUgU c gCAUCAc	334	CauCAaU C AGucuGU
48	GuCGCAU C ACCAAGC	334	cAUcaAU C AGUCugU
63	CcGCCCU C uUGGUGU	338	aAUCAGU C ugUcGAC
71	uUGGUGU U GAACCAa	342	AGUCugU c GACUUCG
96	AGGUGgU C CAGACgG	342	AgUCUGU c GacUuCg
96	AGGUGgU C CaGaCgg	347	gUcGACU U CGAGAUC
96	AGGuGGU C caGAcGG	348	UcGACUU C GAGAUCG
107	ACgGCCU U CCAGCGc	354	UCGAGAU C GACUCUG
108	CgGCCUU C CAGCGcG	354	UCGaGaU C gAcUCUg
122	GCCgGCU A uCCgGAc	354	UCGAGaU c GacUcUg
132	CgGAcgU C AgcGGCG	354	UcGAGAU c GaCUCug
132	cgGAcGU c agCGGCG	359	AuCgACU c ugCCAUu
132	cGGacGU C aGCGGCg	359	AUCGACU C UGCCAUU
156	UGAUGCU C CUcGGCC	359	AuCGAcU C UgCCAuU
159	UGCUCCU c GGCCggG	366	CUGCCAU U GACCUCC
168	GCCggGU C AAGUAcG	372	UUGACCU C CAGAUCA
168	GccGGGU c AaGuacg	372	UuGAccU C CAGAUcA
173	GUCAAGU A cGGGcUG	372	UUGAcCU c cAgaUCa
189	aCaACcU c CAgAuCA	378	UCCAGAU C AACACAg

	189	ACAACcU C CAGAUCA	378	UCCAGAU c AacaCAg
	195	UCCAGAU C AGCCACc	378	UCCAgaU c aACacAG
	206	CACcUGU C CAUCGCC	434	GACUGCU A CCUGgCU
	210	UGUCCAU C GCCAGCA	434	gACUgCU a CCUggCu
5	249	AGaCCAU c GAcGUCg	442	cCUGGcU u UccAUaA
	255	UcGAcGU C gCCAUcC	442	CCUGgCU U UCCAUAA
	261	UCgCCAU c CAGAACG	442	CCUggCU u UCCauAA
	261	ucgCCAU C CAGAaCg	443	CUGgCUU U CCAUAAa
	272	aACgUgU c CGuGgUC	443	CugGcUU u CcauAAA
10	272	AACGUGU C cGUGGUC	444	uGGcuuU c CAUAaAC
	279	CcGUGGU C UUCAAGG	444	UGgCUUU C CAUAAaC
	279	ccGugGU C UuCAAGG	448	UUUCCAU A AaCUGCU
	281	GUGGUCU U CAAGGGG	456	AaCUGCU C CUGCAcC
	282	UGGUCUU C AAGGGGA	465	UGCAcCU C CAgGGGG
15	299	CUGAAcU A caGCUAC	492	gGUGgCU C aaGcAGc
	299	CuGAaCU a cAGCUAc	492	GGUGGcU C AAGCAGC
	492	GGuGGCU c aagCAGC	738	AGGcCuU C CCCCUCC
	492	gGUgGCU c AagCAgc	744	UCCCCCU C CgCgCCU
	503	CAGCUcU U CACAAAc	752	CgCgCCU U CcCGCCC
20	503	CAgcUCU U CAcaaAc	752	CGcGcCU u CCcgCCc
	504	aGCucuU c ACAaACu	753	gCgCCUU C cCGCCCg
	504	AGCUcUU C ACAAAcU	776	GGGGACU C CCGCAUG
	512	ACAAAcU U CAUCUCC	788	AUGCUcU A CUUCUGG
	513	CAAAcUU C AUCUCCU	791	CUcUACU U CUGGUUC
25	516	AcUUCAU C UCCUUCA	792	UcUACUU C UGGUUCU
	518	UUCAUCU C CUUCACC	797	UUCUGGU U CUCcGAu
	521	AUCUCCU U CACCCUG	798	UCUGGUU C UCcGAuC
	521	aUCUcCU U cAcCCUg	800	UGGUUCU C cGAuCaA
	521	aUCUCCU u CAcCcUG	805	CUCcGaU c aAGUGCu
30	522	UCUCCUU C ACCCUGA	818	cUCaACU C cCUGGCC
	537	AGCUGaU u CUGAAGc	836	GccGCcU U CCAGGAg
	552	GACAGgU C UGCAAuG	836	GcCgccU u cCAGgAG
	552	GaCAggU C UgCAaUG	837	CcgCCUU c CAGgaGG
	564	AuGAGAU C AACacCA	837	ccGCcUU C CAGGAgG
35	573	ACacCAU C UCcAACA	852	gCCgUCU C GugCuCA
	573	AcacCAU C UcCAAcA	852	GCCGuCU C gUGCUCA
	575	acCAUCU C cAACAUC	858	UCgUGCU C AGCCUGA

582	cCAACaU C AUggCUg	878	GAuGAGU U CAAGaaA
582	CcAACAU C AUGGCuG	879	AuGAGUU C AAGaaAG
593	GCuGAcU U UGUCCAG	905	caGGGuU U CgACACC
594	CuGAcUU U GUCCAGA	906	aGGGuUU C gACACCA
597	AcUUUGU C CAGACgA	924	AGGAAAU C UUCCAgG
618	CCAGCAU C CUcUCAG	926	GAAAUCU U CCAgGAG
621	GCAUCCU c UCAGAUG	926	GAAaUCU u CcAGGAG
623	AUCCUcU C AGAUGGA	927	AAAUCUU C CAgGAGc
623	aUccUCU c AGAuggA	936	aGgAGCU U UCCAGag
636	GAGACAU c GGGGUGG	937	gGAGCUU u CcagAGg
648	UGGACAU U UCCgUGA	969	CCcAGGU A GCcgUCC
649	GGACAUU U CCgUGAC	969	CCCAgGU a gCCGUCC
650	GACAUUU C CgUGACg	975	UagCCGU C CACUGCC
650	gAcauUU C cGUGAcG	984	ACUGCCU u AAGgUGC
669	ccCCuGU C AUCACAG	985	cuGCcUU A AgGUGCc
672	CuGUCAU C ACAGCCa	999	CCAAGAU C UCCUGCC
672	cuGUCAU c aCAgCcA	1001	AAGAUCU C CUGCCAg
683	GCCAccU a CcUgGAg	1020	gGGGuGU C GUGGUgu
683	GCCaCCU A CCUGGAG	1028	gUGGUGU C UuCUuCc
692	CuggAgU c cCAUCaC	1030	GGUgucU U CUUCcGU
692	CUGGAGU C CCAUCAC	1030	GGUGUCU u CUuCcGu
697	GUCCCAU C ACAAGGG	1034	UCuUcUU C CGUcGcc
706	CAAGGGU C AcUUCAc	1049	GUGAcgU U CCgCUUc
710	GGUCAcU U CAcgcAC	1049	gUGaCgU u CcGCUuC
711	GUCAcUU C AcgcACA	1050	UGAcgUU C CgCUUcC
726	AGAAcGU C UCcGAGG	1055	UUCCgCU U cCCcCGC
728	AAcGUCU C cGAGGcC	1056	UCCgCUU c CCcCGCC
737	GAGgCcU u CcCcCuC	1088	GUgGCcU A CAggUUU
1094	UACAggU U UGAgGAG	1408	CGAGauU a uCACUCu
1095	ACAggUU U GAgGAGG	1408	cGAGAUU A UCACUCu
1105	gGAGGAU A UCaUcAC	1410	AGAUUAU C ACUCucG
1107	AGGAUAU C aUcACcA	1414	UAUCACU C ucGAUGG
1110	auAUcAU C ACCaCcG	1445	AUGGACU U cGGuUUu
1119	CCACcGU C CaGgCCu	1446	UGGACUU c GGuUUuC
1119	CcACCGU C CAGGCCU	1451	UUcGGuU U uCCcaAG
1119	CcAcCgU c cAGGCCu	1452	UcGGuUU u CCcaAGC
1127	cagGCCU C cUacUCC	1474	GGugGAU U UccUgCA

1127	CAGGCCU	C CUAcUCc	1474	GGUGGAU	U UCCUgCA
1130	GCCUCCU	A cUCccAG	1475	GUGGAUU	U CCUgCAG
1133	UCCUAcU	C ccAGAAA	1476	UGGAUUU	C CUgCAGA
1146	AAaagCU	C UUcCuAC	1529	gACGuCU	C cGcCCAu
1146	AAAAGCU	C UUCcUAc	1529	GAcGUCU	C CgccCAu
1148	AAGCUCU	U CcUAcaC	1549	UgGagGU	c aGGgagU
1149	AGCUCUU	C cUAcaCC	1580	GAUGGCU	c CCaaCUc
1152	UCUUCcU	A caCCUCU	1580	gaUGGCU	C CCAACUC
1158	UAcaCCU	C UUGGAUU	1587	CCCAACU	C CUuCugu
1160	caCCUCU	U GGAUUUC	1595	CUucUGU	c CuGaaGa
1165	CuUGgAU	u UCCAguG	1595	CUuCUgU	c CUgAagA
1165	CUUGGAU	U UCCAGug	1595	cuuCUgU	C CUgAAGa
1166	UUGGAUU	U CCAGugc	1624	GCAgCAU	a CccUgGg
1166	UUGGaUU	u ccAGUgC	1694	uCcGGaU	C cCAGCUG
1245	AGgCUGU	U UCCAACc	1787	cCuGGCU	u uAGcCUG
1246	GgCUGUU	U CCAACcU	1788	CUGGCuU	U AgccUGC
1247	gCuGuuU	C CaACCUG	1816	gCuAaAU	c UCuCuGG
1247	gCUGUUU	C CAACcUG	1818	UaAAUCU	C UcuGGCu
1247	gcUGUUU	c CAaCCug	1818	uAAaucU	C UcUgGCU
1268	AGCcGCU	C CGAGUCC	1828	UggCUGU	C UcUCucU
1274	UCCGAGU	C CcUgCAG	1847	CUcaAGU	a AAcGAau
1286	CAGAGCU	c uCUcCgc			
1302	cCCUGAU	c gCCAcGg			
1317	UGGGCAU	C CCgGAGG			
1326	CgGAGGU	C AUGUCUC			
1331	GUCAUGU	C UCGGCUC			
1333	CAUGUCU	C GGCUCGA			
1338	CUCGGCU	C GAGGUgG			
1349	GuGGCgU	u CaCAGCC			
1349	GUgGcGU	U cACAGCC			
1350	UgGcGUU	c ACAGCCC			
1350	UGGcGuU	c acAGCcc			
1359	CAGCCCU	C AUGAACA			
1383	UGgaCCU	C UUCGAaA			
1385	gaCCUCU	U CGAaAUC			
1386	aCCUCUU	C GAaAUCA			
1392	UCGAaAU	C AUCAACC			

1395	AaAUCAU C AACCCcG	
1407	CcGAGAU U AUCACUC	

Table V: Rabbit CETP Hammerhead Ribozyme Sequence

nt. Position	Ribozyme Sequence	
20	CUCGUAG	CUGAUGAGGCCGAAAGGCCGAA AGGCGCC
23	AGCCUCG	CUGAUGAGGCCGAAAGGCCGAA AGGAGGC
23	AGCCUCG	CUGAUGAGGCCGAAAGGCCGAA AGGAGGC
36	GACACAC	CUGAUGAGGCCGAAAGGCCGAA AUGCCAG
43	GUGAUGC	CUGAUGAGGCCGAAAGGCCGAA ACACACG
43	GUGAUGC	CUGAUGAGGCCGAAAGGCCGAA ACACACG
48	GCUUGGU	CUGAUGAGGCCGAAAGGCCGAA AUGCGAC
63	ACACCAA	CUGAUGAGGCCGAAAGGCCGAA AGGGCGG
71	UUGGUUC	CUGAUGAGGCCGAAAGGCCGAA ACACCAA
96	CCGUCUG	CUGAUGAGGCCGAAAGGCCGAA ACCACCU
96	CCGUCUG	CUGAUGAGGCCGAAAGGCCGAA ACCACCU
96	CCGUCUG	CUGAUGAGGCCGAAAGGCCGAA ACCACCU
107	GCGCUGG	CUGAUGAGGCCGAAAGGCCGAA AGGCCGU
108	CGCGCUG	CUGAUGAGGCCGAAAGGCCGAA AAGGCCG
122	GUCCGGA	CUGAUGAGGCCGAAAGGCCGAA AGCCGGC
132	CGCCGCU	CUGAUGAGGCCGAAAGGCCGAA ACGUCCG
132	CGCCGCU	CUGAUGAGGCCGAAAGGCCGAA ACGUCCG
132	CGCCGCU	CUGAUGAGGCCGAAAGGCCGAA ACGUCCG
156	GGCCGAG	CUGAUGAGGCCGAAAGGCCGAA AGCAUCA
159	CCCGGCC	CUGAUGAGGCCGAAAGGCCGAA AGGAGCA
168	CGUACUU	CUGAUGAGGCCGAAAGGCCGAA ACCCGGC
168	CGUACUU	CUGAUGAGGCCGAAAGGCCGAA ACCCGGC
173	CAGCCCG	CUGAUGAGGCCGAAAGGCCGAA ACUUGAC
189	UGAUCUG	CUGAUGAGGCCGAAAGGCCGAA AGGUUGU
189	UGAUCUG	CUGAUGAGGCCGAAAGGCCGAA AGGUUGU
195	GGUGGCU	CUGAUGAGGCCGAAAGGCCGAA AUCUGGA
206	GGCGAUG	CUGAUGAGGCCGAAAGGCCGAA ACAGGUG
210	UGCUGGC	CUGAUGAGGCCGAAAGGCCGAA AUGGACA
249	CGACGUC	CUGAUGAGGCCGAAAGGCCGAA AUGGUCU
255	GGAUGGC	CUGAUGAGGCCGAAAGGCCGAA ACGUCGA
261	CGUUCUG	CUGAUGAGGCCGAAAGGCCGAA AUGGCGA

	261	CGUUCUG	CUGAUGAGGCCGAAAGGCCGAA AUGGCGA
	272	GACCACG	CUGAUGAGGCCGAAAGGCCGAA ACACGUU
	272	GACCACG	CUGAUGAGGCCGAAAGGCCGAA ACACGUU
	279	CCUUGAA	CUGAUGAGGCCGAAAGGCCGAA ACCACGG
5	279	CCUUGAA	CUGAUGAGGCCGAAAGGCCGAA ACCACGG
	281	CCCCUUG	CUGAUGAGGCCGAAAGGCCGAA AGACCAC
	282	UCCCCUU	CUGAUGAGGCCGAAAGGCCGAA AAGACCA
	299	GUAGCUG	CUGAUGAGGCCGAAAGGCCGAA AGUUCAG
	299	GUAGCUG	CUGAUGAGGCCGAAAGGCCGAA AGUUCAG
10	305	ACUCGUG	CUGAUGAGGCCGAAAGGCCGAA AGCUGUA
	305	ACUCGUG	CUGAUGAGGCCGAAAGGCCGAA AGCUGUA
	305	ACUCGUG	CUGAUGAGGCCGAAAGGCCGAA AGCUGUA
	323	GAUGCCC	CUGAUGAGGCCGAAAGGCCGAA ACCCCCA
	330	ACUGAUU	CUGAUGAGGCCGAAAGGCCGAA AUGCCCA
15	334	ACAGACU	CUGAUGAGGCCGAAAGGCCGAA AUUGAUG
	334	ACAGACU	CUGAUGAGGCCGAAAGGCCGAA AUUGAUG
	338	GUCGACA	CUGAUGAGGCCGAAAGGCCGAA ACUGAUU
	342	CGAAGUC	CUGAUGAGGCCGAAAGGCCGAA ACAGACU
	342	CGAAGUC	CUGAUGAGGCCGAAAGGCCGAA ACAGACU
20	347	GAUCUCG	CUGAUGAGGCCGAAAGGCCGAA AGUCGAC
	348	CGAUCUC	CUGAUGAGGCCGAAAGGCCGAA AAGUCGA
	354	CAGAGUC	CUGAUGAGGCCGAAAGGCCGAA AUCUCGA
	354	CAGAGUC	CUGAUGAGGCCGAAAGGCCGAA AUCUCGA
	354	CAGAGUC	CUGAUGAGGCCGAAAGGCCGAA AUCUCGA
25	354	CAGAGUC	CUGAUGAGGCCGAAAGGCCGAA AUCUCGA
	359	AAUGGCA	CUGAUGAGGCCGAAAGGCCGAA AGUCGAU
	359	AAUGGCA	CUGAUGAGGCCGAAAGGCCGAA AGUCGAU
	359	AAUGGCA	CUGAUGAGGCCGAAAGGCCGAA AGUCGAU
	366	GGAGGUC	CUGAUGAGGCCGAAAGGCCGAA AUGGCAG
30	372	UGAUCUG	CUGAUGAGGCCGAAAGGCCGAA AGGUCAA
	372	UGAUCUG	CUGAUGAGGCCGAAAGGCCGAA AGGUCAA
	372	UGAUCUG	CUGAUGAGGCCGAAAGGCCGAA AGGUCAA
	378	CUGUGUU	CUGAUGAGGCCGAAAGGCCGAA AUCUGGA
	378	CUGUGUU	CUGAUGAGGCCGAAAGGCCGAA AUCUGGA
35	378	CUGUGUU	CUGAUGAGGCCGAAAGGCCGAA AUCUGGA
	434	AGCCAGG	CUGAUGAGGCCGAAAGGCCGAA AGCAGUC
	434	AGCCAGG	CUGAUGAGGCCGAAAGGCCGAA AGCAGUC

442	UUAUGGA	CUGAUGAGGCCGAAAGGCCGAA AGCCAGG
442	UUAUGGA	CUGAUGAGGCCGAAAGGCCGAA AGCCAGG
442	UUAUGGA	CUGAUGAGGCCGAAAGGCCGAA AGCCAGG
443	UUUAUGG	CUGAUGAGGCCGAAAGGCCGAA AAGCCAG
443	UUUAUGG	CUGAUGAGGCCGAAAGGCCGAA AAGCCAG
444	GUUUAUG	CUGAUGAGGCCGAAAGGCCGAA AAAGCCA
444	GUUUAUG	CUGAUGAGGCCGAAAGGCCGAA AAAGCCA
448	AGCAGUU	CUGAUGAGGCCGAAAGGCCGAA AUGGAAA
456	GGUGCAG	CUGAUGAGGCCGAAAGGCCGAA AGCAGUU
465	CCCCCUG	CUGAUGAGGCCGAAAGGCCGAA AGGUGCA
492	GCUGCUU	CUGAUGAGGCCGAAAGGCCGAA AGCCACC
492	GCUGCUU	CUGAUGAGGCCGAAAGGCCGAA AGCCACC
492	GCUGCUU	CUGAUGAGGCCGAAAGGCCGAA AGCCACC
492	GCUGCUU	CUGAUGAGGCCGAAAGGCCGAA AGCCACC
503	GUUUGUG	CUGAUGAGGCCGAAAGGCCGAA AGAGCUG
503	GUUUGUG	CUGAUGAGGCCGAAAGGCCGAA AGAGCUG
504	AGUUUGU	CUGAUGAGGCCGAAAGGCCGAA AAGAGCU
504	AGUUUGU	CUGAUGAGGCCGAAAGGCCGAA AAGAGCU
512	GGAGAUG	CUGAUGAGGCCGAAAGGCCGAA AGUUUGU
513	AGGAGAU	CUGAUGAGGCCGAAAGGCCGAA AAGUUUG
516	UGAAGGA	CUGAUGAGGCCGAAAGGCCGAA AUGAAGU
518	GGUGAAG	CUGAUGAGGCCGAAAGGCCGAA AGAUGAA
521	CAGGGUG	CUGAUGAGGCCGAAAGGCCGAA AGGAGAU
521	CAGGGUG	CUGAUGAGGCCGAAAGGCCGAA AGGAGAU
521	CAGGGUG	CUGAUGAGGCCGAAAGGCCGAA AGGAGAU
522	UCAGGGU	CUGAUGAGGCCGAAAGGCCGAA AAGGAGA
537	GCUUCAG	CUGAUGAGGCCGAAAGGCCGAA AUCAGCU
552	CAUUGCA	CUGAUGAGGCCGAAAGGCCGAA ACCUGUC
552	CAUUGCA	CUGAUGAGGCCGAAAGGCCGAA ACCUGUC
564	UGGUGUU	CUGAUGAGGCCGAAAGGCCGAA AUCUCAU
573	UGUUGGA	CUGAUGAGGCCGAAAGGCCGAA AUGGUGU
573	UGUUGGA	CUGAUGAGGCCGAAAGGCCGAA AUGGUGU
575	GAUGUUG	CUGAUGAGGCCGAAAGGCCGAA AGAUGGU
582	CAGCCAU	CUGAUGAGGCCGAAAGGCCGAA AUGUUGG
582	CAGCCAU	CUGAUGAGGCCGAAAGGCCGAA AUGUUGG
593	CUGGACA	CUGAUGAGGCCGAAAGGCCGAA AGUCAGC
594	UCUGGAC	CUGAUGAGGCCGAAAGGCCGAA AAGUCAG

	597	UCGUCUG	CUGAUGAGGCCGAAAGGCCGAA ACAAAGU
	618	CUGAGAG	CUGAUGAGGCCGAAAGGCCGAA AUGCUGG
	621	CAUCUGA	CUGAUGAGGCCGAAAGGCCGAA AGGAUGC
	623	UCCAUCU	CUGAUGAGGCCGAAAGGCCGAA AGAGGAU
5	623	UCCAUCU	CUGAUGAGGCCGAAAGGCCGAA AGAGGAU
	636	CCACCCC	CUGAUGAGGCCGAAAGGCCGAA AUGUCUC
	648	UCACGGA	CUGAUGAGGCCGAAAGGCCGAA AUGUCCA
	649	GUCACGG	CUGAUGAGGCCGAAAGGCCGAA AAUGUCC
	650	CGUCACG	CUGAUGAGGCCGAAAGGCCGAA AAAUGUC
10	650	CGUCACG	CUGAUGAGGCCGAAAGGCCGAA AAAUGUC
	669	CUGUGAU	CUGAUGAGGCCGAAAGGCCGAA ACAGGGG
	672	UGGCUGU	CUGAUGAGGCCGAAAGGCCGAA AUGACAG
	672	UGGCUGU	CUGAUGAGGCCGAAAGGCCGAA AUGACAG
	683	CUCCAGG	CUGAUGAGGCCGAAAGGCCGAA AGGUGGC
15	683	CUCCAGG	CUGAUGAGGCCGAAAGGCCGAA AGGUGGC
	692	GUGAUGG	CUGAUGAGGCCGAAAGGCCGAA ACUCCAG
	692	GUGAUGG	CUGAUGAGGCCGAAAGGCCGAA ACUCCAG
	697	CCCUUGU	CUGAUGAGGCCGAAAGGCCGAA AUGGGAC
	706	GUGAAGU	CUGAUGAGGCCGAAAGGCCGAA ACCCUUG
20	710	GUGCGUG	CUGAUGAGGCCGAAAGGCCGAA AGUGACC
	711	UGUGCGU	CUGAUGAGGCCGAAAGGCCGAA AAGUGAC
	726	CCUCGGA	CUGAUGAGGCCGAAAGGCCGAA ACGUUCU
	728	GGCCUCG	CUGAUGAGGCCGAAAGGCCGAA AGACGUU
	737	GAGGGGG	CUGAUGAGGCCGAAAGGCCGAA AGGCCUC
25	738	GGAGGGG	CUGAUGAGGCCGAAAGGCCGAA AAGGCCU
	744	AGGCGCG	CUGAUGAGGCCGAAAGGCCGAA AGGGGGA
	752	GGGCGGG	CUGAUGAGGCCGAAAGGCCGAA AGGCGCG
	752	GGGCGGG	CUGAUGAGGCCGAAAGGCCGAA AGGCGCG
	753	CGGGCGG	CUGAUGAGGCCGAAAGGCCGAA AAGGCGC
30	776	CAUGCGG	CUGAUGAGGCCGAAAGGCCGAA AGUCCCC
	788	CCAGAAG	CUGAUGAGGCCGAAAGGCCGAA AGAGCAU
	791	GAACCAG	CUGAUGAGGCCGAAAGGCCGAA AGUAGAG
	792	AGAACCA	CUGAUGAGGCCGAAAGGCCGAA AAGUAGA
	797	AUCGGAG	CUGAUGAGGCCGAAAGGCCGAA ACCAGAA
35	798	GAUCGGA	CUGAUGAGGCCGAAAGGCCGAA AACCAGA
	800	UUGAUCG	CUGAUGAGGCCGAAAGGCCGAA AGAACCA
	805	AGCACUU	CUGAUGAGGCCGAAAGGCCGAA AUCGGAG

818	GGCCAGG	CUGAUGAGGCCGAAAGGCCGAA AGUUGAG
836	CUCCUGG	CUGAUGAGGCCGAAAGGCCGAA AGGCGGC
836	CUCCUGG	CUGAUGAGGCCGAAAGGCCGAA AGGCGGC
837	CCUCCUG	CUGAUGAGGCCGAAAGGCCGAA AAGGCGG
837	CCUCCUG	CUGAUGAGGCCGAAAGGCCGAA AAGGCGG
852	UGAGCAC	CUGAUGAGGCCGAAAGGCCGAA AGACGGC
852	UGAGCAC	CUGAUGAGGCCGAAAGGCCGAA AGACGGC
858	UCAGGCU	CUGAUGAGGCCGAAAGGCCGAA AGCACGA
878	UUUCUUG	CUGAUGAGGCCGAAAGGCCGAA ACUCAUC
879	CUUUCUU	CUGAUGAGGCCGAAAGGCCGAA AACUCAU
905	GGUGUCG	CUGAUGAGGCCGAAAGGCCGAA AACCCUG
906	UGGUGUC	CUGAUGAGGCCGAAAGGCCGAA AAACCCU
924	CCUGGAA	CUGAUGAGGCCGAAAGGCCGAA AUUUCCU
926	CUCCUGG	CUGAUGAGGCCGAAAGGCCGAA AGAUUUC
926	CUCCUGG	CUGAUGAGGCCGAAAGGCCGAA AGAUUUC
927	GCUCCUG	CUGAUGAGGCCGAAAGGCCGAA AAGAUUU
936	CUCUGGA	CUGAUGAGGCCGAAAGGCCGAA AGCUCCU
937	CCUCUGG	CUGAUGAGGCCGAAAGGCCGAA AAGCUCC
969	GGACGGC	CUGAUGAGGCCGAAAGGCCGAA ACCUGGG
969	GGACGGC	CUGAUGAGGCCGAAAGGCCGAA ACCUGGG
975	GGCAGUG	CUGAUGAGGCCGAAAGGCCGAA ACGGCUA
984	GCACCUU	CUGAUGAGGCCGAAAGGCCGAA AGGCAGU
985	GGCACCU	CUGAUGAGGCCGAAAGGCCGAA AAGGCAG
999	GGCAGGA	CUGAUGAGGCCGAAAGGCCGAA AUCUUGG
1001	CUGGCAG	CUGAUGAGGCCGAAAGGCCGAA AGAUCUU
1020	ACACCAC	CUGAUGAGGCCGAAAGGCCGAA ACACCCC
1028	GGAAGAA	CUGAUGAGGCCGAAAGGCCGAA ACACCAC
1030	ACGGAAG	CUGAUGAGGCCGAAAGGCCGAA AGACACC
1030	ACGGAAG	CUGAUGAGGCCGAAAGGCCGAA AGACACC
1034	GGCGACG	CUGAUGAGGCCGAAAGGCCGAA AAGAAGA
1049	GAAGCGG	CUGAUGAGGCCGAAAGGCCGAA ACGUCAC
1049	GAAGCGG	CUGAUGAGGCCGAAAGGCCGAA ACGUCAC
1050	GGAAGCG	CUGAUGAGGCCGAAAGGCCGAA AACGUCA
1055	GCGGGGG	CUGAUGAGGCCGAAAGGCCGAA AGCGGAA
1056	GGCGGGG	CUGAUGAGGCCGAAAGGCCGAA AAGCGGA
1088	AAACCUG	CUGAUGAGGCCGAAAGGCCGAA AGGCCAC
1094	CUCCUCA	CUGAUGAGGCCGAAAGGCCGAA ACCUGUA

1095	CCUCCUC	CUGAUGAGGCCGAAAGGCCGAA AACCUGU
1105	GUGAUGA	CUGAUGAGGCCGAAAGGCCGAA AUCCUCC
1107	UGGUGAU	CUGAUGAGGCCGAAAGGCCGAA AUAUCCU
1110	CGGUGGU	CUGAUGAGGCCGAAAGGCCGAA AUGAUAU
1119	AGGCCUG	CUGAUGAGGCCGAAAGGCCGAA ACGGUGG
1119	AGGCCUG	CUGAUGAGGCCGAAAGGCCGAA ACGGUGG
1119	AGGCCUG	CUGAUGAGGCCGAAAGGCCGAA ACGGUGG
1127	GGAGUAG	CUGAUGAGGCCGAAAGGCCGAA AGGCCUG
1127	GGAGUAG	CUGAUGAGGCCGAAAGGCCGAA AGGCCUG
1130	CUGGGAG	CUGAUGAGGCCGAAAGGCCGAA AGGAGGC
1133	UUUCUGG	CUGAUGAGGCCGAAAGGCCGAA AGUAGGA
1146	GUAGGAA	CUGAUGAGGCCGAAAGGCCGAA AGCUUUU
1146	GUAGGAA	CUGAUGAGGCCGAAAGGCCGAA AGCUUUU
1148	GUGUAGG	CUGAUGAGGCCGAAAGGCCGAA AGAGCUU
1149	GGUGUAG	CUGAUGAGGCCGAAAGGCCGAA AAGAGCU
1152	AGAGGUG	CUGAUGAGGCCGAAAGGCCGAA AGGAAGA
1158	AAUCCAA	CUGAUGAGGCCGAAAGGCCGAA AGGUGUA
1160	GAAAUCC	CUGAUGAGGCCGAAAGGCCGAA AGAGGUG
1165	CACUGGA	CUGAUGAGGCCGAAAGGCCGAA AUCCAAG
1165	CACUGGA	CUGAUGAGGCCGAAAGGCCGAA AUCCAAG
1166	GCACUGG	CUGAUGAGGCCGAAAGGCCGAA AAUCCAA
1166	GCACUGG	CUGAUGAGGCCGAAAGGCCGAA AAUCCAA
1245	GGUUGGA	CUGAUGAGGCCGAAAGGCCGAA ACAGCCU
1246	AGGUUGG	CUGAUGAGGCCGAAAGGCCGAA AACAGCC
1247	CAGGUUG	CUGAUGAGGCCGAAAGGCCGAA AAACAGC
1247	CAGGUUG	CUGAUGAGGCCGAAAGGCCGAA AAACAGC
1247	CAGGUUG	CUGAUGAGGCCGAAAGGCCGAA AAACAGC
1268	GGACUCG	CUGAUGAGGCCGAAAGGCCGAA AGCGGCU
1274	CUGCAGG	CUGAUGAGGCCGAAAGGCCGAA ACUCGGA
1286	GCGGAGA	CUGAUGAGGCCGAAAGGCCGAA AGCUCUG
1290	GGGAGCG	CUGAUGAGGCCGAAAGGCCGAA AGAGAGC
1302	CCGUGGC	CUGAUGAGGCCGAAAGGCCGAA AUCAGGG
1317	CCUCCGG	CUGAUGAGGCCGAAAGGCCGAA AUGCCCA
1326	GAGACAU	CUGAUGAGGCCGAAAGGCCGAA ACCUCCG
1331	GAGCCGA	CUGAUGAGGCCGAAAGGCCGAA ACAUGAC
1333	UCGAGCC	CUGAUGAGGCCGAAAGGCCGAA AGACAUG
1338	CCACCUC	CUGAUGAGGCCGAAAGGCCGAA AGCCGAG

1349	GGCUGUG	CUGAUGAGGCCGAAAGGCCGAA ACGCCAC
1349	GGCUGUG	CUGAUGAGGCCGAAAGGCCGAA ACGCCAC
1350	GGGCUGU	CUGAUGAGGCCGAAAGGCCGAA AACGCCA
1350	GGGCUGU	CUGAUGAGGCCGAAAGGCCGAA AACGCCA
1359	UGUUCAU	CUGAUGAGGCCGAAAGGCCGAA AGGGCUG
1383	UUUCGAA	CUGAUGAGGCCGAAAGGCCGAA AGGUCCA
1385	GAUUUCG	CUGAUGAGGCCGAAAGGCCGAA AGAGGUC
1386	UGAUUUC	CUGAUGAGGCCGAAAGGCCGAA AAGAGGU
1392	GGUUGAU	CUGAUGAGGCCGAAAGGCCGAA AUUUCGA
1395	CGGGGUU	CUGAUGAGGCCGAAAGGCCGAA AUGAUUU
1407	GAGUGAU	CUGAUGAGGCCGAAAGGCCGAA AUCUCGG
1408	AGAGUGA	CUGAUGAGGCCGAAAGGCCGAA AAUCUCG
1408	AGAGUGA	CUGAUGAGGCCGAAAGGCCGAA AAUCUCG
1410	CGAGAGU	CUGAUGAGGCCGAAAGGCCGAA AUAAUCU
1414	CCAUCGA	CUGAUGAGGCCGAAAGGCCGAA AGUGAUA
1445	AAAACCG	CUGAUGAGGCCGAAAGGCCGAA AGUCCAU
1446	GAAAACC	CUGAUGAGGCCGAAAGGCCGAA AAGUCCA
1451	CUUGGGA	CUGAUGAGGCCGAAAGGCCGAA AACCGAA
1452	GCUUGGG	CUGAUGAGGCCGAAAGGCCGAA AAACCGA
1474	UGCAGGA	CUGAUGAGGCCGAAAGGCCGAA AUCCACC
1474	UGCAGGA	CUGAUGAGGCCGAAAGGCCGAA AUCCACC
1475	CUGCAGG	CUGAUGAGGCCGAAAGGCCGAA AAUCCAC
1476	UCUGCAG	CUGAUGAGGCCGAAAGGCCGAA AAAUCCA
1529	AUGGGCG	CUGAUGAGGCCGAAAGGCCGAA AGACGUC
1529	AUGGGCG	CUGAUGAGGCCGAAAGGCCGAA AGACGUC
1549	ACUCCCU	CUGAUGAGGCCGAAAGGCCGAA ACCUCCA
1580	GAGUUGG	CUGAUGAGGCCGAAAGGCCGAA AGCCAUC
1580	GAGUUGG	CUGAUGAGGCCGAAAGGCCGAA AGCCAUC
1587	ACAGAAG	CUGAUGAGGCCGAAAGGCCGAA AGUUGGG
1595	UCUUCAG	CUGAUGAGGCCGAAAGGCCGAA ACAGAAG
1595	UCUUCAG	CUGAUGAGGCCGAAAGGCCGAA ACAGAAG
1595	UCUUCAG	CUGAUGAGGCCGAAAGGCCGAA ACAGAAG
1624	CCCAGGG	CUGAUGAGGCCGAAAGGCCGAA AUGCUGC
1694	CAGCUGG	CUGAUGAGGCCGAAAGGCCGAA AUCCGGA
1787	CAGGCUA	CUGAUGAGGCCGAAAGGCCGAA AGCCAGG
1788	GCAGGCU	CUGAUGAGGCCGAAAGGCCGAA AAGCCAG
1816	CCAGAGA	CUGAUGAGGCCGAAAGGCCGAA AUUUAGC

1818	AGCCAGA CUGAUGAGGCCGAAAGGCCGAA AGAUUUA
1818	AGCCAGA CUGAUGAGGCCGAAAGGCCGAA AGAUUUA
1828	AGAGAGA CUGAUGAGGCCGAAAGGCCGAA ACAGCCA
1847	AUUCGUU CUGAUGAGGCCGAAAGGCCGAA ACUUGAG

Table VI: Human CETP Hairpin Ribozyme and Substrate Sequence

nt. Position	Ribozyme Sequence	Substrate
27	UUCCGGGC AGAA GGGUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	AGACCCU GCU GCCCGGAA
30	CUCUUCCG AGAA GCAGGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCCUGCU GCC CGGAAGAG
96	GUGGCCCG AGAA GUUCAG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CUGAACG GCU CGGGCCAC
119	GGUUAUCA AGAA GUGGUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CACCACU GCC UGAUAACC
145	AGGGUCAG AGAA GUGGCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGCCACA GUC CUGACCCU
150	GGGCCAGG AGAA GGACUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CAGUCCU GAC CCUGGCCC
162	CAUUGCCC AGAA GGGCCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGGCCCU GCU GGGCAAUG
182	GCCUUUGG AGAA GGCAUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CAUGCCU GCU CCAAAGGC
235	ACCAGGAG AGAA GGCUUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CAAGCCU GCC CUCCUGGU
276	GGAAGGCG AGAA GGAUCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGAUCCA GAC CGCCUUCC
280	CGCUGGAA AGAA GUCUGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCAGACC GCC UUCCAGCG
369	AGUGGCUG AGAA GGAUGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	ACAUCCA GAU CAGCCACU
490	AGCCACCA AGAA GUGGUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CACCACU GCC UGGUGGCU
513	AGUCAAUG AGAA GAUCAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UUGAUCA GUC CAUUGACU
552	GUGUGUUG AGAA GGAGGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	ACCUCCA GAU CAACACAC
564	CACAGGUC AGAA GUGUGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	ACACACA GCU GACCUGUG
567	AGUCACAG AGAA GCUGUG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CACAGCU GAC CUGUGACU

	591	GGGCAUCG AGAA GCACUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAGUGCG GAC CGAUGCCC
	595	UCAGGGGC AGAA GUCCGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCGGACC GAU GCCCCUGA
	604	AGGUAGCA AGAA GGGGCA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UGCCCCU GAC UGCUACCU
	615	UAUGGAAA AGAA GGUAGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GCUACCU GUC UUUCCAUA
5	630	GAUGCAGG AGAA GCUUAU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AUAAGCU GCU CCUGCAUC
	675	UUGUGAAC AGAA GCUUGA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCAAGCA GCU GUUCACAA
	678	AAUUUGUG AGAA GCUGCU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGCAGCU GUU CACAAAUU
	726	CUUUGCAG AGAA GUCCCU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGGGACA GAU CUGCAAAG
	766	UGGACAAA AGAA GCCAUG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CAUGGCC GAU UUUGUCCA
10	802	AUGUCUCC AGAA GAAAGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCUUUCA GAU GGAGACAU
	853	AGGUAGGA AGAA GUGAUG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CAUCACA GCC UCCUACCU
	942	AGUCCCCC AGAA GUGUGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCACACU GCU GGGGGACU
	1025	GAGCAUGA AGAA GCCAUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAUGGCC GCC UCAUGCUC
	1037	UCCCAUCA AGAA GAGCAU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AUGCUCA GCC UGAUGGGA
15	1041	CGUCUCCC AGAA GGCUGA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCAGCCU GAU GGGAGACG
	1121	GCUGGGGA AGAA GCCGAC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GUCGGCG GCU UCCCCAGC
	1147	AGGCAGUG AGAA GUGACU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGUCACC GUC CACUGCCU
	1154	CAUCUUGA AGAA GUGGAC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GUCCACU GCC UCAAGAUG
	1240	UGUUGCUG AGAA GGGCGU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA ACGCCCA GAC CAGCAACA
20	1291	GAGGCCUG AGAA GUAGUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GACUACC GUC CAGGCCUC

1344	UUGGUGUA AGAA GGAAAU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	AUUUCCA GAU UACACCAA
1360	AAGUUGGA AGAA GUCUUU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	AAAGACU GUU UCCAACUU
1382	GGACUCGG AGAA GCUCUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GAGAGCA GCU CCGAGUCC
1423	AUGCCCAC AGAA GUGAUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GAUCACC GCU GUGGGCAU
1452	CUACCUCG AGAA GAGACA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGUCUCG GCU CGAGGUAG
1471	UUCAUGAG AGAA GUAAAC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GUUUACA GCC CUCAUGAA
1545	UCUGCAGC AGAA GGAAGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GCUUCCU GCU GCUGCAGA
1548	CCAUCUGC AGAA GCAGGA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UCCUGCU GCU GCAGAUGG
1554	CAAAGUCC AGAA GCAGCA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGCUGCA GAU GGACUUUG
1581	AAUCCACC AGAA GGUGCU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	AGCACCU GCU GGUGGAUU
1669	AGGGUUCC AGAA GUGAGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GCUCACA GCU GGAACCCU

Table VII: Rabbit CETP Hairpin Ribozyme and Substrate Sequences

nt. Position	Ribozyme Sequence		Substrate
57	ACCAAGAG AGAA GGCUUG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CAAGCCC GCC CUCUUGGU
98	GGAAGGCC AGAA GGACCA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGGUCCA GAC GGCCUUCC
102	CGCUGGAA AGAA GUCUGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCAGACG GCC UUCCAGCG
126	CCGCUGAC AGAA GGAUAG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CUAUCCG GAC GUCAGCGG
160	CUUGACCC AGAA GAGGAG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CUCCUCG GCC GGGUCAAG

	191	GGUGGCUG AGAA GGAGGU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	ACCUCCA GAU CAGCCACC
	203	UGGCGAUG AGAA GGUGGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GCCACCU GUC CAUCGCCA
	335	AGUCGACA AGAA GAUUGA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UCAAUCA GUC UGUCGACU
	339	UCGAAGUC AGAA GACUGA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UCAGUCU GUC GACUUCGA
5	374	CUGUGUUG AGAA GGAGGU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	ACCUCCA GAU CAACACAG
	389	CGUCGCAG AGAA GCUCUG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CAGAGCU GAC CUGCGACG
	426	AGGUAGCA AGAA GGGGCA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGCCCCC GAC UGCUACCU
	452	GGUGCAGG AGAA GUUUAU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	AUAAACU GCU CCUGCACC
	497	UUGUGAAG AGAA GCUUGA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UCAAGCA GCU CUUCACAA
10	533	GCUUCAGA AGAA GCUUCA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGAAGCU GAU UCUGAAGC
	588	UGGACAAA AGAA GCCAUG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CAUGGCU GAC UUUGUCCA
	599	CGGCCCUC AGAA GGACAA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UUGUCCA GAC GAGGGCCG
	624	AUGUCUCC AGAA GAGAGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCUCUCA GAU GGAGACAU
	755	GAAGACCG AGAA GGAAGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCUUCCC GCC CGGUCUUC
15	760	CCCCAGAA AGAA GGGCGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCGCCCG GUC UUCUGGGG
	801	AGCACUUG AGAA GAGAAC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GUUCUCC GAU CAAGUGCU
	831	UCCUGGAA AGAA GCCCUG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CAGGGCC GCC UUCCAGGA
	847	GAGCACGA AGAA GCCCUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GAGGGCC GUC UCGUGCUC
	859	CCCUGUCA AGAA GAGCAC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GUGCUCA GCC UGACAGGG
20	972	AGGCAGUG AGAA GCUACC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GGUAGCC GUC CACUGCCU

979	CACCUUAA	AGAA	GUGGAC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GUCCACU	GCC UUAAGGUG
1035	GUCACGGC	AGAA	GAAGAA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UUCUUCC	GUC GCCGUGAC
1051	GCGGGGGA	AGAA	GAACGU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	ACGUUCC	GCU UCCCCCGC
1060	GCCAUCUG	AGAA	GGGGAA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UUCCCCC	GCC CAGAUGGC
1065	UCUCGGCC	AGAA	GGGCGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCGCCCA	GAU GGCCGAGA
1116	GAGGCCUG	AGAA	GUGGUG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CACCACC	GUC CAGGCCUC
1198	AUUUGCUG	AGAA	GCCUGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GCAGGCA	GCU CAGCAAAU
1242	AGGUUGGA	AGAA	GCCUUA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UAAGGCU	GUU UCCAACCU
1253	GGCUCUCA	AGAA	GGUUGG	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	CCAACCU	GAC UGAGAGCC
1264	GGACUCGG	AGAA	GCUCUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GAGAGCC	GCU CCGAGUCC
1291	GAUCAGGG	AGAA	GAGAGA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UCUCUCC	GCU CCCUGAUC
1298	CCGUGGCG	AGAA	GGGAGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GCUCCCU	GAU CGCCACGG
1334	CCACCUCG	AGAA	GAGACA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGUCUCG	GCU CGAGGUGG
1353	UUCAUGAG	AGAA	GUGAAC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GUUCACA	GCC CUCAUGAA
1423	CAGCAGCA	AGAA	GCCAUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GAUGGCU	GCC UGCUGCUG
1427	UCUGCAGC	AGAA	GGCAGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GCUGCCU	GCU GCUGCAGA
1430	CCAUCUGC	AGAA	GCAGGC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GCCUGCU	GCU GCAGAUGG
1436	CGAAGUCC	AGAA	GCAGCA	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	UGCUGCA	GAU GGACUUCG
1447	CUUGGGAA	AGAA	GAAGUC	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	GACUUCG	GUU UUCCCAAG
1463	AAUCCACC	AGAA	GGUGCU	ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA	AGCACCU	GCU GGUGGAUU

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1521  GCGGAGAC AGAA GCGUGU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA ACACGCU GAC GUCUCCGC
1530  CCCCGAUG AGAA GAGACG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CGUCUCC GCC CAUCGGGG
1592  GUCUUCAG AGAA GAAGGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCCUUCU GUC CUGAAGAC
1690  CAGCUGGG AGAA GGAGCA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UGCUCCG GAU CCCAGCUG
1697  UAGCAGGC AGAA GGGAUC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GAUCCCA GCU GCCUGCUA
1700  CGUUAGCA AGAA GCUGGG ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA CCCAGCU GCC UGCUAACG
1727  ACCAGCAC AGAA GCUCCC ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA GGGAGCA GCC GUGCUGGU
1763  GGACCUCA AGAA GGGUCU ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA AGACCCA GAC UGAGGUCC
1793  ACUCACUG AGAA GGCUAA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UUAGCCU GCC CAGUGAGU
1825  CAGAGAGA AGAA GCCAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCUGGCU GUC UCUCUCUG
1835  ACUUGAGA AGAA GAGAGA ACCAGAGAAACACACGUUGUGGUACAUUACCUGGUA UCUCUCU GCC UCUCAAGU
```

Claims

1. Nucleic acid molecule which blocks synthesis and/or expression of mRNAs associated with initial development, progression or regression of vascular disease.

2. The nucleic acid of claim 1 wherein said molecule is an enzymatic nucleic acid molecule.

3. The nucleic acid molecule of claim 2 wherein said nucleic acid molecule cleaves mRNA produced from the gene encoding CETP.

4. The nucleic acid molecule of claim 2, wherein the binding arms of said enzymatic nucleic acid molecule which contain sequences complementary to the sequences defined in any one of Tables II, IV, VI and VII.

5. The enzymatic nucleic acid molecule of claims 2 or 3 or 4, wherein said nucleic acid molecule is in a hammerhead motif.

6. The enzymatic nucleic acid molecule of claim 2 or 3 or 4, wherein said nucleic acid molecule is in a hairpin, hepatitis Delta virus, group I intron, VS nucleic acid or RNaseP nucleic acid motif.

7. The enzymatic nucleic acid molecule of any of claims 2 or 3 or 4, wherein said ribozyme comprises between 12 and 100 bases complementary to the RNA of said region.

8. The enzymatic nucleic acid of claim 7, wherein said ribozyme comprises between 14 and 24 bases complementary to the RNA of said region.

9. Enzymatic nucleic acid molecule consisting essentially of any sequence selected from the group of those shown in Tables III, V, VI and VII.

10. A mammalian cell including an enzymatic nucleic acid molecule of any of claims 1 or 2 or 3.

11. The cell of claim 10, wherein said cell is a human cell.

12. An expression vector comprising nucleic acid encoding the enzymatic nucleic acid molecule of any of claims 2 or 3 or 4, in a manner which allows expression and/or delivery of that enzymatic nucleic acid molecule within a mammalian cell.

13. A mammalian cell including an expression vector of claim 12.

14. The cell of claim 13, wherein said cell is a human cell.

15. A method for treatment of a patient having a condition associated with the level of CETP activity, wherein the said condition is selected from the group consisting of familial-hypercholestremia, atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, vascular complications of diabetes, transplant, atherectomy and angioplastic restenosis, wherein said patient is administered a therapeutically effective amount of an enzymatic nucleic acid molecule of claims 2 or 3 or 4.

16. A method for treatment of a condition related to the level of CETP activity by administering to a patient an expression vector of claim 12.

17. The method of claims 15 or 16, wherein said patient is a human.

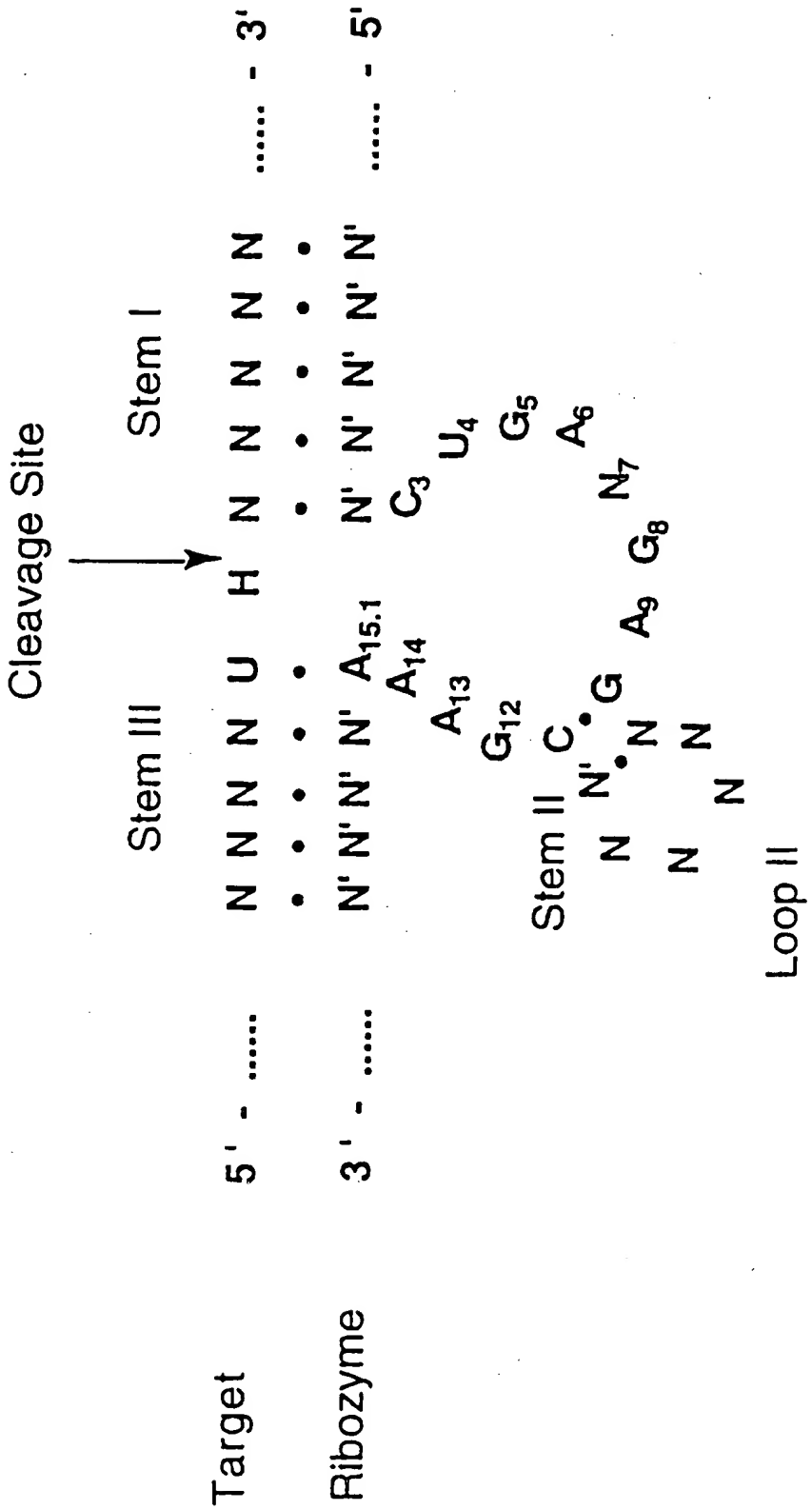
Cleavage Site
Stem I
Stem III
Stem II
Loop II
Target
Ribozyme
5' - .....
3' - .....
..... - 3'
..... - 5'
N N N N U H N N N N N
N' N' N' N' A15.1 N' N' N' N' N'
A14
A13
G12
C3
U4
G5
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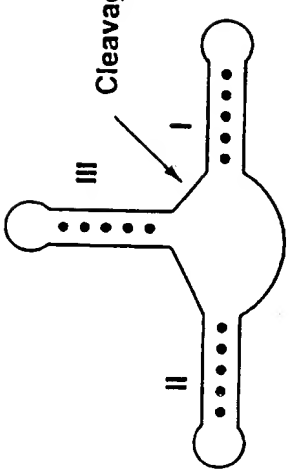
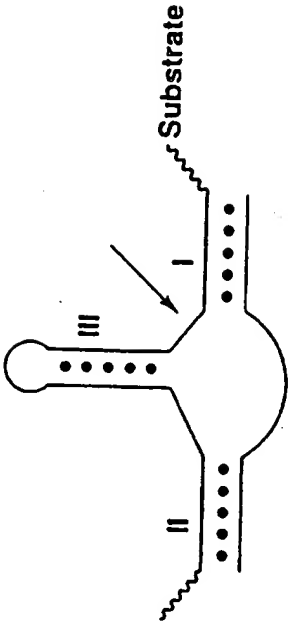
FIG. 1.

FIG. 2a.



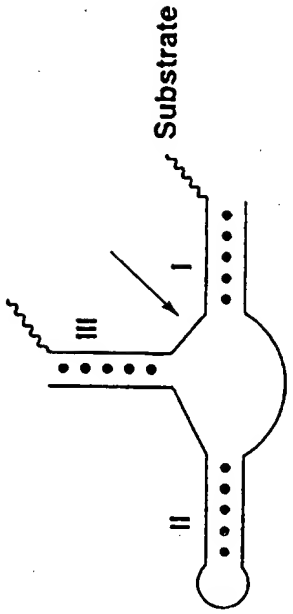
a

FIG. 2b.



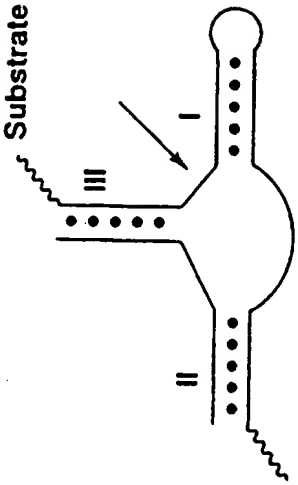
b

FIG. 2c.



c

FIG. 2d.



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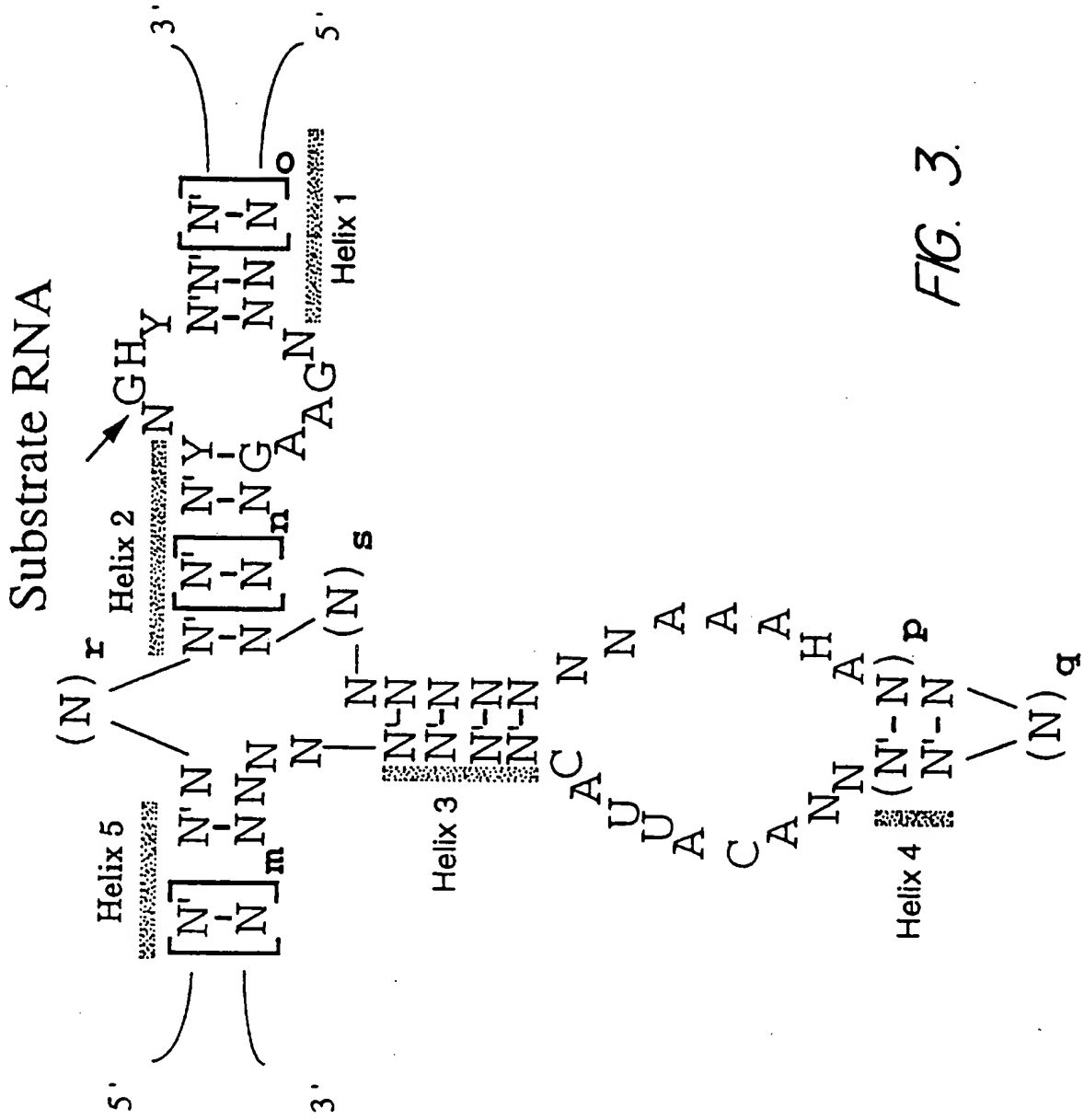


FIG. 3.

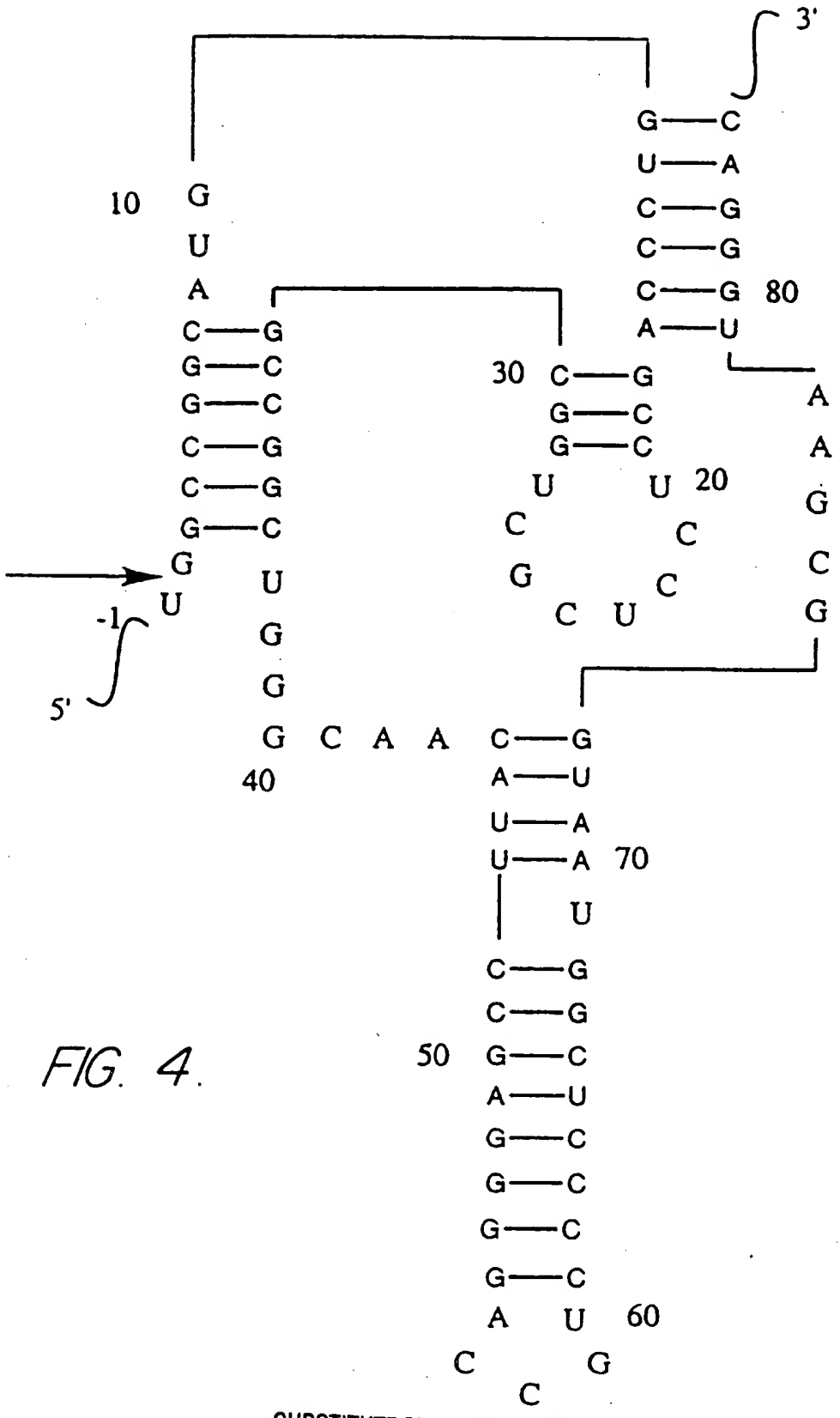
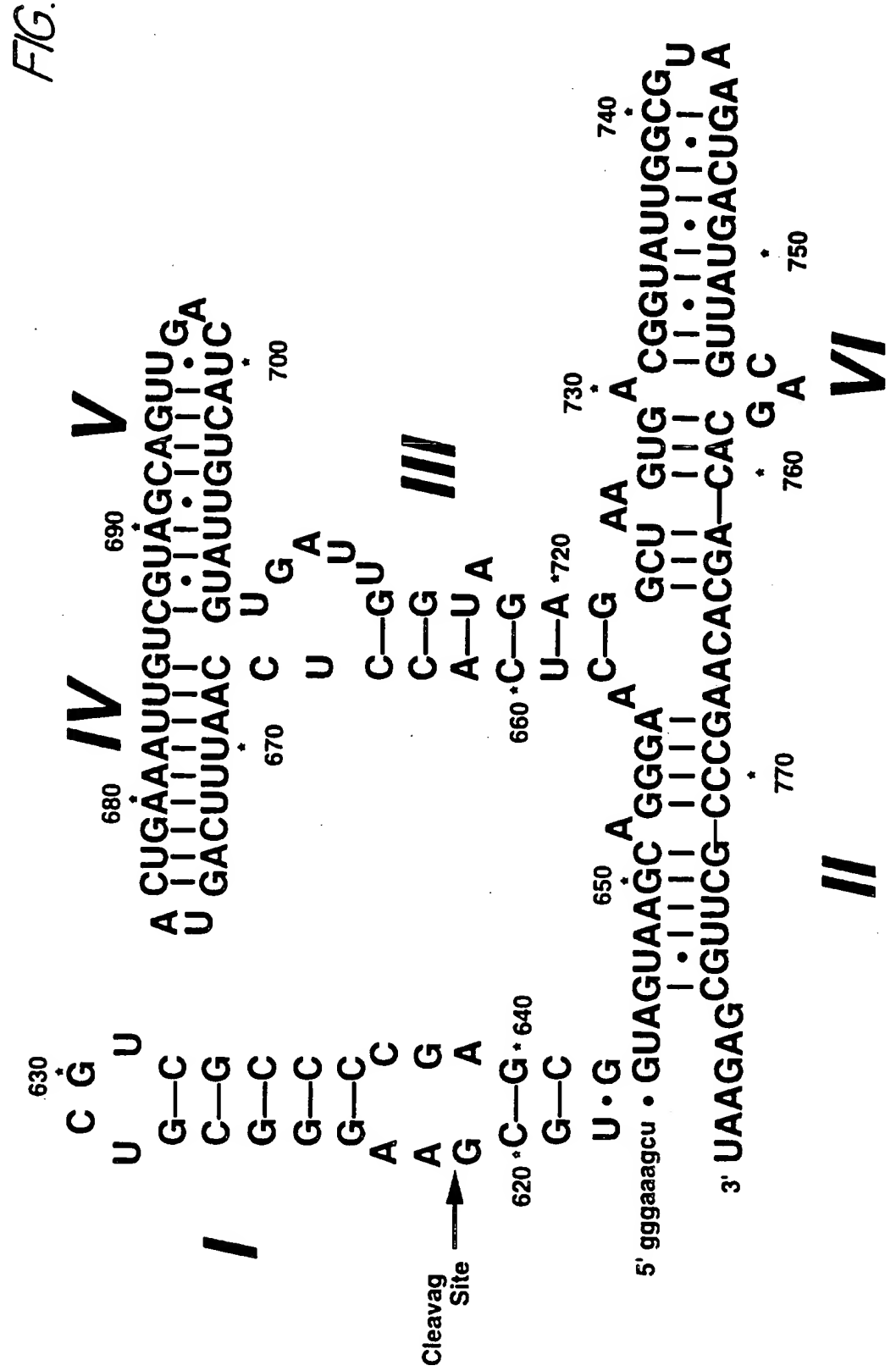


FIG. 4.

FIG. 5.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II
III
IV
V
VI
Cleavag Site
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650
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720
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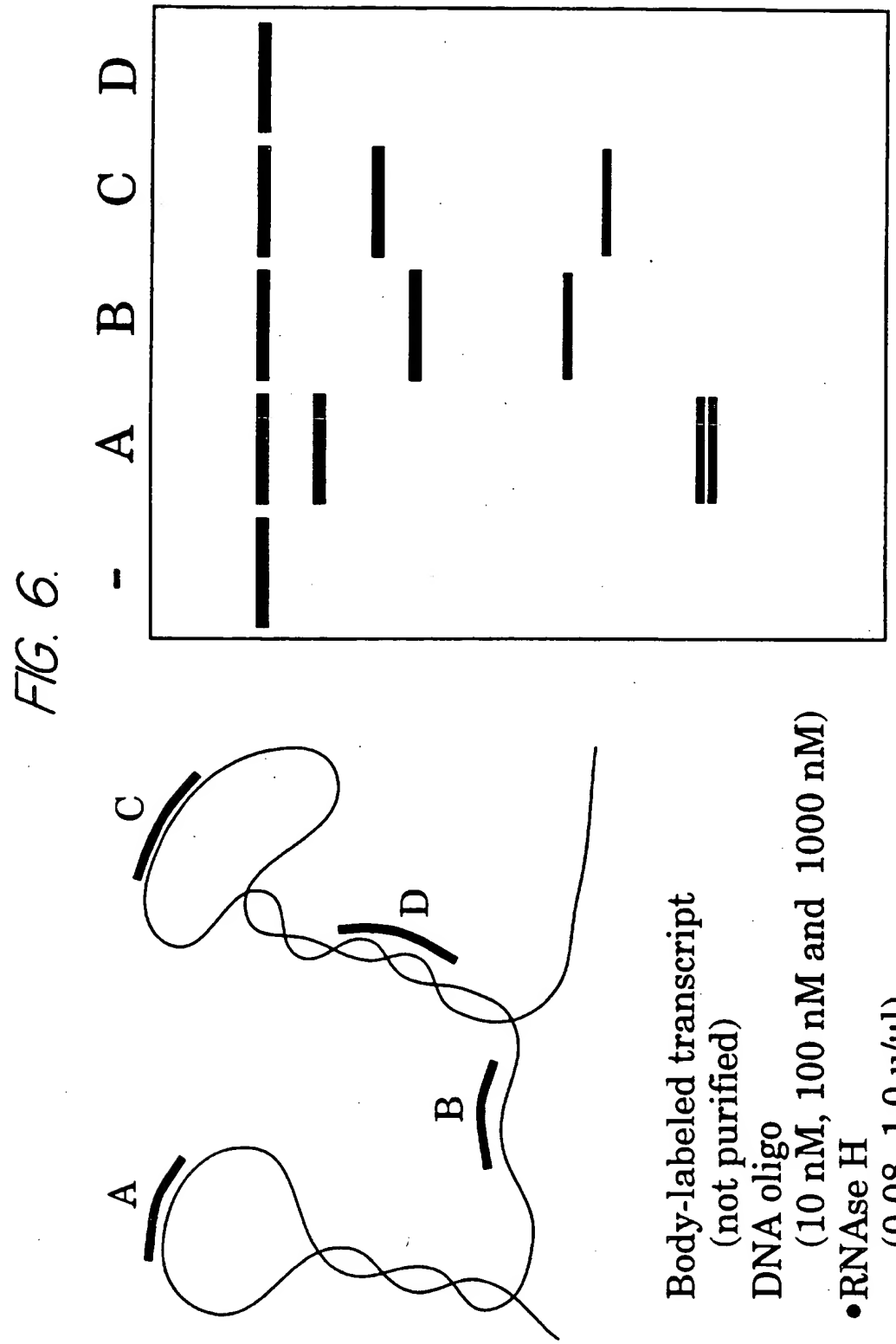
750
760
770

FIG. 6.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A
B
C
D
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(not purified)
DNA oligo
(10 nM, 100 nM and 1000 nM)
•RNAse H
(0.08 -1.0 u/µl)
37°C, 10 min

INTERNATIONAL SEARCH REPORT

Int[illegible]tional Application No
PCT/US 95/16000

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/52 C12N9/00 A61K31/70 C07H21/02 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 02595 (RIBOZYME PHARMACEUTICALS INC) 3 February 1994 cited in the application see page 13, line 23 - line 35	1,2,5-8, 10-14
Y	see page 21, line 9 - page 25 see claims	1-17

Y	LIPIDS, vol. 29, December 1994, pages 811-818, XP000568834 BISGAIER, C. ET AL.: "Cholesteryl ester transfer protein inhibition by PD 140195" cited in the application see the whole document	1-17

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 May 1996	10.05.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Andres, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NATURE, vol. 327, 18 June 1987, LONDON GB, pages 632-634, XP002001819 DRAYNA, D. ET AL.: "Cloning and sequencing of human cholesteryl ester transfer protein cDNA" cited in the application ---	
P,X	JOURNAL OF BIOCHEMISTRY AND MOLECULAR BIOLOGY 28 (3). 243-248, 31 May 1995, XP000569967 LEE, M. ET AL.: "Inhibitory effects of antisense RNA on expression of cholesteryl ester transfer protein in vaccinia virus expression system." see the whole document -----	1

1

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US95/16000

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15-17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/16000

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9402595	03-02-94	AU-B-	4769893	14-02-94
		CA-A-	2140343	03-02-94
		EP-A-	0654077	24-05-95
		JP-T-	7509133	12-10-95